STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number

TO:	From:
Hector Reyes Location: REM-5A18&5C18 Art Unit: 1625 Thursday, June 24, 2004 Case Serial Number: 10/649380	Alex Waclawiw Location: Biotech-Chem Library Rem 1A71 Phone: 272-2534 Alexandra.waclawiw@uspto.gov

Search Notes

1244 81

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Reyes, Hector   Examiner #: 78264   Date: 6/12/04

Art Unit: 1625   Phone Number 30 Rem5A26   Serial Number: 10/649380

Mail Box and Bldg Room Location: 272-0691   Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: see bibs. copy

Inventors (please provide full names): ↓

Earliest Priority Filing Date:

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search a Nateglinide having the properties described in claim (x ray pattern).

other crystalline structure for the said compound?

Thanks

Hector Reyes

STAFF USE ONLY		Type of Search		Vendors and cost where applicable	
Searcher	Point of Contact:	NA Sequence (#)		STN	
Searcher Phone #	Alexandra Waclawiw Technical Info. Specialist	AA Sequence (#)		Dialog	
Searcher Location	CM1 6A12 Tel. 308-4491	Structure (#)	1	Questel/Orbit	
Date Searcher Picked Up	6-24-04	Bibliographic		Dr.Link	
Date Completed	6-24-04	Litigation		Lexis/Nexis	
Searcher Prep & Review Time	10	Fulltext		Sequence Systems	
Clerical Prep Time		Patent Family		WWW/Internet	
Online Time	25	Other		Other (specify)	

PTO-1590 (8-01)

=> d his

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                ACT HECTOR/A
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L1              STR
L2           35 SEA FILE=REGISTRY FAM FUL L1
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     FILE 'CAPLUS' ENTERED AT 08:30:13 ON 24 JUN 2004
L3          288 S L2
                SET SFIELD BI
L4      1858686 S CRYST?
L5       152529 S POLYMORPH?
L6       727199 S X RAY
L7           25 S L3 AND L4
L8           10 S L3 AND  L5
L9           14 S L3 AND L6
L10          26 S L7 OR L8 OR L9
L11          25 S L10 AND L4
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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:   23 JUN 2004  HIGHEST RN 698346-19-9
DICTIONARY FILE UPDATES:  23 JUN 2004  HIGHEST RN 698346-19-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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L1                STR
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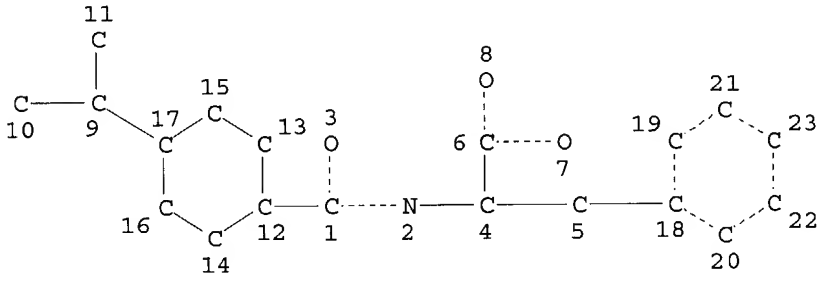


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  23

STEREO ATTRIBUTES: NONE
L2            35 SEA FILE=REGISTRY FAM FUL L1

100.0% PROCESSED    396 ITERATIONS                          35 ANSWERS
SEARCH TIME: 00.00.01


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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 24 Jun 2004 VOL 140 ISS 26
FILE LAST UPDATED: 23 Jun 2004 (20040623/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L5       152529 SEA FILE=CAPLUS ABB=ON  PLU=ON  POLYMORPH?
L6       727199 SEA FILE=CAPLUS ABB=ON  PLU=ON  X RAY
L7           25 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 AND L4
L8           10 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 AND  L5
L9           14 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3 AND L6
L10          26 SEA FILE=CAPLUS ABB=ON  PLU=ON  L7 OR L8 OR L9
L11          25 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10 AND L4


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L11  ANSWER 1 OF 25  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2004:203799  CAPLUS
DOCUMENT NUMBER:          140:241062
TITLE:                    Process for the formation of a crystalline
                          polymorphic form of nateglinide
INVENTOR(S):              Reguri, Buchi Reddy; Kadaboina, Rajasekhar;
                          Polavarapu, Srinivas
PATENT ASSIGNEE(S):       Reddy's Laboratories Limited, India; Reddy's
                          Laboratories, Inc.
SOURCE:                   PCT Int. Appl., 29 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
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     WO 2004020396      A1   20040311      WO 2003-US26880  20030827
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
             TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY,
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KG, KZ, MD, RU
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004077725 A1 20040422 US 2003-649380 20030827
PRIORITY APPLN. INFO.: IN 2002-MA631 A 20020828

AB A **crystalline polymorphic** form of nateglinide are described and its **X-ray** diffraction pattern presented.

IC ICM C07C233-63
ICS C07C231-24

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 34, 75

ST **crystal polymorphism** nateglinide

IT **Crystallization**
(in a process for the formation of a **crystalline polymorphic** form of nateglinide)

IT Drug delivery systems
(oral; process for the formation of a **crystalline polymorphic** form of nateglinide)

IT **Polymorphism** (**crystal**)
(process for the formation of a **crystalline polymorphic** form of nateglinide)

IT Aromatic hydrocarbons, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvents; in a process for the formation of a **crystalline polymorphic** form of nateglinide)

IT Drug delivery systems
(tablets; process for the formation of a **crystalline polymorphic** form of nateglinide)

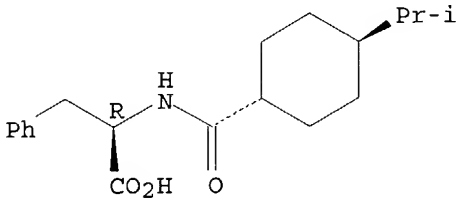
IT 95-47-6, o-Xylene, uses
RL: NUU (Other use, unclassified); USES (Uses)
(process for the formation of a **crystalline polymorphic** form of nateglinide)

IT **105816-04-4P**, Nateglinide
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(process for the formation of a **crystalline polymorphic** form of nateglinide)

IT **105816-04-4P**, Nateglinide
RL: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(process for the formation of a **crystalline polymorphic** form of nateglinide)

RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:80637 CAPLUS
DOCUMENT NUMBER: 140:151932
TITLE: Preparation of **polymorphic** forms of nateglinide
INVENTOR(S): Yahalomi, Ronit; Shapior, Evgeny; Dolitzky, Ben-zion; Gozlan, Yigael; Gome, Boaz
PATENT ASSIGNEE(S): Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceutical Usa, Inc.
SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009532	A1	20040129	WO 2003-US22375	20030718
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004116526	A1	20040617	US 2003-623237	20030718

PRIORITY APPLN. INFO.:

US 2002-396904P	P	20020718
US 2002-413622P	P	20020925
US 2002-414199P	P	20020926
US 2002-423750P	P	20021105
US 2002-432093P	P	20021210
US 2002-432962P	P	20021212
US 2003-442109P	P	20030123
US 2003-449791P	P	20030224
US 2003-479016P	P	20030616
US 2003-614266	A	20030703

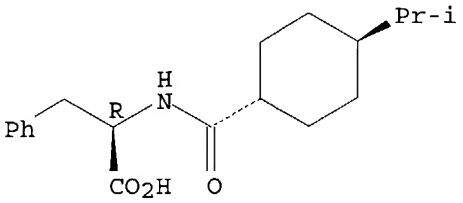
AB The invention discloses the preparation of 26 characterized forms of nateglinide (forms A, C, D, F, G, I, J, K, L, M, N, O, P, Q, T, U, V, Y, α, β, γ, δ, ε, σ, θ and Ω). Most of the forms are solvates (with the exception of forms L, P, U, α, δ and σ). **Polymorphic** forms are characterized by their mp, DSC, XRPD, FTIR; form interconversion is also discussed. For example, D-phenylalanine is reacted with trans-[[4-(isopropyl)cyclohexanee]carbonyl]chloride (i. NaOHaq; ii. H2SO4). The wet cake of nateglinide is dissolved in EtOAc, the aqueous phase is removed and the resulting solution heated to 50° under reduced pressure and added to hot heptane. The resulting solution is cooled and seeded with the B-form to afford the δ-form (33% yield).

IC ICM C07C231-24
ICS C07C233-63; A61K031-16; A61P003-00
CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 75
ST **polymorphic** nateglinide blood sugar lowering prepn
IT Fluidized beds
(dryers; preparation of **polymorphic** forms of nateglinide)
IT Drying apparatus
(fluidized-bed; preparation of **polymorphic** forms of nateglinide)
IT Solvents
(nateglinide solvate; preparation of **polymorphic** forms of nateglinide)
IT **Crystal** nucleation
Crystallization
Human
Polymorphism (**crystal**)
Slurries
(preparation of **polymorphic** forms of nateglinide)
IT 50-99-7, D-Glucose, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(blood, lowering, treatment; preparation of **polymorphic** forms of nateglinide)
IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 67-64-1, Acetone, uses 71-23-8, n-Propanol, uses 71-36-3, n-Butanol, uses 75-05-8, Acetonitrile, uses 75-52-5, Nitromethane, uses 78-93-3, Methyl ethyl ketone, uses 108-10-1, Methyl isobutyl ketone 108-88-3, Toluene, uses 110-54-3, Hexane, uses 141-78-6, Ethyl acetate, uses 142-82-5, Heptane, uses 563-80-4, Methyl isopropyl ketone 1330-20-7, Xylene, uses
RL: NUU (Other use, unclassified); USES (Uses)
(nateglinide solvate; preparation of **polymorphic** forms of nateglinide)
IT 67-66-3, Chloroform, uses 109-99-9, Tetrahydrofuran, uses 123-91-1, Dioxane, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of **polymorphic** forms of nateglinide)
IT **105816-04-4P**, Nateglinide
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(preparation of **polymorphic** forms of nateglinide)
IT **105816-04-4DP**, Nateglinide, **polymorphs**
651353-42-3P 651353-43-4P 651353-44-5P
651353-45-6P 651353-46-7P 651353-47-8P
651353-48-9P 651353-49-0P 651353-50-3P
651353-51-4P 651353-52-5P 651353-53-6P
651353-54-7P
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of **polymorphic** forms of nateglinide)
IT 673-06-3, D-Phenylalanine 84855-54-9, trans-[[4-(Isopropyl)cyclohexane]carbonyl]chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **polymorphic** forms of nateglinide)
IT **105816-04-4P**, Nateglinide
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(preparation of **polymorphic** forms of nateglinide)
RN 105816-04-4 CAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **105816-04-4DP**, Nateglinide, **polymorphs**
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651353-45-6P 651353-46-7P 651353-47-8P
651353-48-9P 651353-49-0P 651353-50-3P
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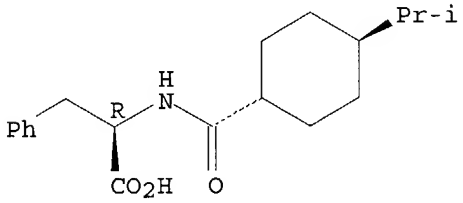
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of **polymorphic** forms of nateglinide)

RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

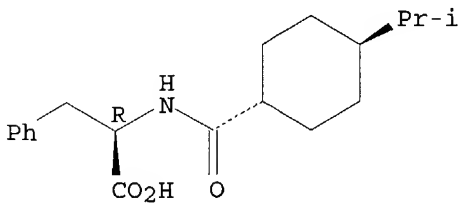


RN 651353-42-3 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with methanol (9CI) (CA INDEX NAME)

CM 1

CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 67-56-1
CMF C H4 O

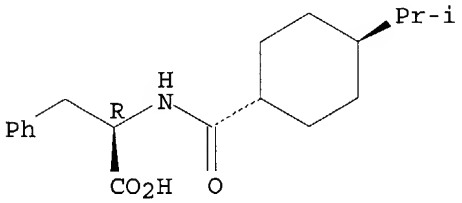
H_3C-OH

RN 651353-43-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with ethanol (9CI) (CA INDEX NAME)

CM 1

CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 64-17-5
CMF C2 H6 O

H_3C-CH_2-OH

RN 651353-44-5 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1-butanol (9CI) (CA INDEX NAME)

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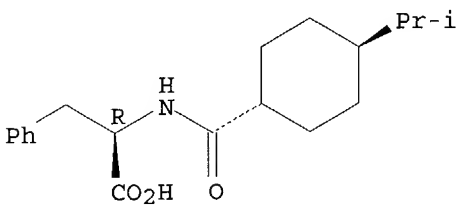
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



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CRN 71-36-3
CMF C4 H10 O

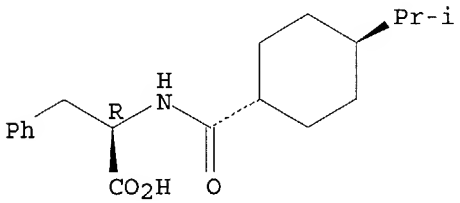
$H_3C-CH_2-CH_2-CH_2-OH$

RN 651353-45-6 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1-propanol (9CI) (CA INDEX NAME)

CM 1

CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 71-23-8
CMF C3 H8 O

$H_3C-CH_2-CH_2-OH$

RN 651353-46-7 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with N,N-dimethylacetamide (9CI) (CA INDEX NAME)

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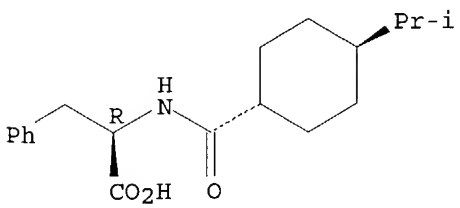
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



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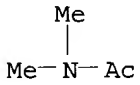
CMF C4 H9 N O



RN 651353-47-8 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1-methyl-2-pyrrolidinone (9CI) (CA INDEX NAME)

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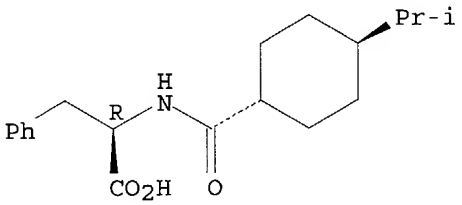
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



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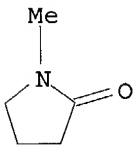

RN 651353-48-9 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with N,N-dimethylformamide (9CI) (CA INDEX NAME)

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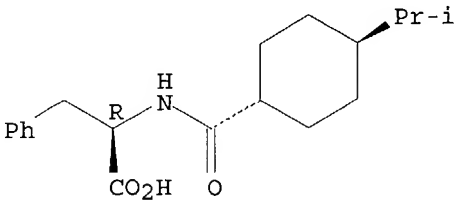
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



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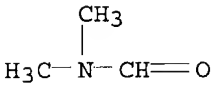
CRN 68-12-2
CMF C3 H7 N O

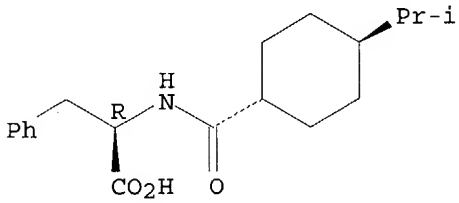


RN 651353-49-0 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1,2-dimethoxyethane (9CI) (CA INDEX NAME)

CM 1

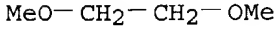
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 110-71-4
CMF C4 H10 O2

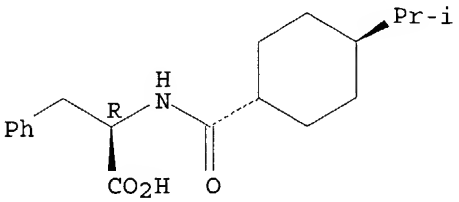


RN 651353-50-3 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with dimethylbenzene (9CI) (CA INDEX NAME)

CM 1

CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 1330-20-7
CMF C8 H10
CCI IDS

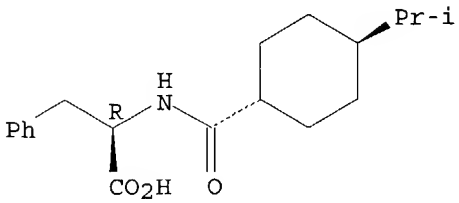
2 (D1—Me)

RN 651353-51-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with tetrachloromethane (9CI) (CA INDEX NAME)

CM 1

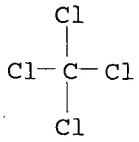
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 56-23-5
CMF C Cl4

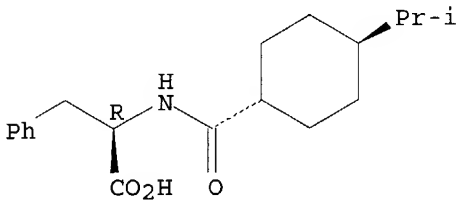


RN 651353-52-5 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with 1,2-dichloroethane (9CI) (CA INDEX NAME)

CM 1

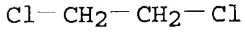
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 107-06-2
CMF C2 H4 Cl2

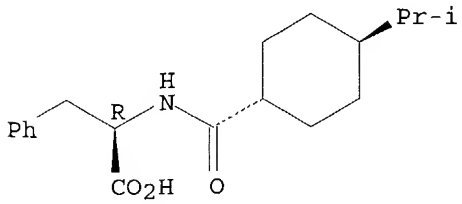


RN 651353-53-6 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with trichloromethane (9CI) (CA INDEX NAME)

CM 1

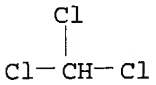
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 67-66-3
CMF C H Cl3

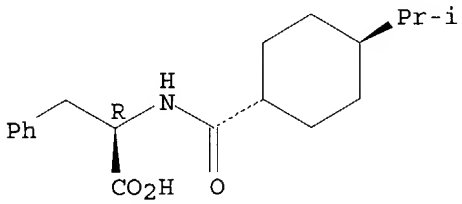


RN 651353-54-7 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, compd. with heptane (9CI) (CA INDEX NAME)

CM 1

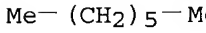
CRN 105816-04-4
CMF C19 H27 N O3

Absolute stereochemistry. Rotation (-).



CM 2

CRN 142-82-5
CMF C7 H16



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:892741 CAPLUS
DOCUMENT NUMBER: 139:369757
TITLE: Process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide)
INVENTOR(S): Rajamahendra, Shanmughasamy; Aswathanarayanappa, Chandrashekar; Puthiaparampil, Tom Thomas; Sridharan, Madhavan; Ganesh, Sambasivam
PATENT ASSIGNEE(S): Biocon India Limited, India
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003093222	A1	20031113	WO 2002-IN114	20020429

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2002-IN114 20020429

AB Novel **polymorph** Form C of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (I; i.e., nateglinide) is produced having a different IR spectrum and **X-ray** diffraction patterns (presented) from previously known forms of I.

IC ICM C07C233-63
ICS A61K031-198

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 34, 75

ST nateglinide prepn **crystal polymorphism**; isopropylcyclohexylcarbonylphenylalanine prepn **crystal polymorphism**

IT Drying
Filtration
(in a process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT Bases, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(in a process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT Acids, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(inorg.; in a process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT Diabetes mellitus
(non-insulin-dependent; process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide) for the treatment of)

IT Antidiabetic agents
Polymorphism (**crystal**)
(process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT Ligroine
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT 1344-28-1, Alumina, uses
RL: NUU (Other use, unclassified); USES (Uses)
(base support; in a process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT 110-86-1, Pyridine, reactions 121-44-8, Triethylamine, reactions

NRA

497-19-8, Sodium carbonate, reactions 584-08-7, Potassium carbonate 1310-58-3, Potassium hydroxide, reactions 1310-65-2, Lithium hydroxide 1310-73-2, Sodium hydroxide, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(base; in a process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT 7077-05-6, trans-4-Isopropylcyclohexanecarboxylic acid 13033-84-6, D-Phenylalanine methyl ester hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(in a process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT 71760-04-8, Propanephosphonic acid anhydride
RL: RGT (Reagent); RACT (Reactant or reagent)
(mineral acid; in a process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

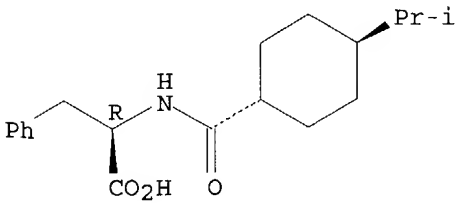
IT **105816-04-4P**, Nateglinide
RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PREP (Preparation); PROC (Process)
(process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-63-0, Isopropanol, uses 75-09-2, Dichloromethane, uses 141-78-6, Ethyl acetate, uses 1300-21-6, Dichloroethane 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

IT **105816-04-4P**, Nateglinide
RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PREP (Preparation); PROC (Process)
(process for the preparation of a **crystal polymorphic** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (nateglinide))

RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:837030 CAPLUS
DOCUMENT NUMBER: 139:341723

TITLE: Novel nateglinide **crystals**
INVENTOR(S): Koguchi, Yoshihito; Nakao, Tomoko; Sumikawa, Michito
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003087039	A1	20031023	WO 2003-JP4686	20030414

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2002-111963 A 20020415

AB A type **crystal** (powder **X-ray** diffraction main peaks: 4.4°, 5.2°, 15.7°, 18.5° (2 theta)), M type **crystal** (powder **X-ray** diffraction main peaks: 6.0°, 14.2°, 15.2°, 18.8° (2 theta)), and P type **crystal** (powder **X-ray** diffraction main peaks: 4.8°, 5.3°, 14.3°, 15.2° (2 theta)) of nateglinide, which are all novel **crystals**, can be prepared by a method comprising dissolving nateglinide in a solvent exhibiting high solubility for nateglinide and then adding a solvent exhibiting poor solubility for nateglinide or dissolving nateglinide in a mixed solvent comprising a solvent exhibiting high solubility for nateglinide and a solvent exhibiting poor solubility for nateglinide and then cooling the resulting nateglinide solution to precipitate **crystals**, subjecting the product to filtration, and then drying at a specific temperature Nateglinide is a known antidiabetic.

IC ICM C07C233-63
ICS C07C231-24
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 75
ST nateglinide **crystal** prepn antidiabetic
IT **Crystal** structure
(**crystal** structure of nateglinide **crystals**)
IT Antidiabetic agents
Crystal structure types
Drying
Polymorphism (**crystal**)
(preparation of A, M, and P type nateglinide **crystals** and drying of said **crystals**)
IT **Crystallization**
(preparation of A, M, and P type nateglinide **crystals** by **crystallization** from mixture of solvents)
IT **105816-04-4P**, Nateglinide
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of A, M, and P type nateglinide **crystals** by

NPL

crystallization from mixture of solvents)

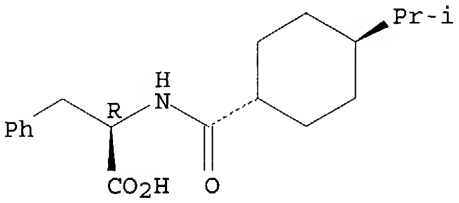
IT 64-17-5, Ethanol, uses 67-64-1, Acetone, uses 75-09-2, Methylene chloride, uses 110-54-3, Hexane, uses 123-91-1, Dioxane, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent for **crystallization**; preparation of A, M, and P type nateglinide **crystals** by **crystallization** from mixture of solvents)

IT **105816-04-4P**, Nateglinide
RL: PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of A, M, and P type nateglinide **crystals** by **crystallization** from mixture of solvents)

RN 105816-04-4 CAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:837029 CAPLUS

DOCUMENT NUMBER: 139:328379

TITLE: **Crystal polymorphism** of nateglinide

INVENTOR(S): Sutton, Paul Allen

PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis Pharma G.m.b.H.

SOURCE: PCT Int. Appl., 10 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003087038	A1	20031023	WO 2003-EP3864	20030414

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

PRIORITY APPLN. INFO.: US 2002-372625P P 20020415

AB New **crystal** forms of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (i.e., nateglinide) are produced by dissolving nateglinide in any of its forms, including solvates, in an organic solvent to form a solution followed by precipitation of nateglinide from the solution, and isolating and

NPA

drying the precipitated **crystal** form of nateglinide. The precipitation of nateglinide may be induced either by cooling the solution, or by addition of another solvent which is miscible with the first solvent but in which nateglinide is only poorly soluble, or by combination of the two. Depending on the solvent a specific **crystal** form of nateglinide may be obtained, e.g., the R'-type **crystal** form of nateglinide produced by the described method has a different m.p., infra red spectra and **X-ray** diffraction patterns from the previously known **crystal** forms of nateglinide.

IC ICM C07C233-63
ICS C07C231-22

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 34, 75

ST nateglinide **crystal polymorphism**

IT **Polymorphism** (**crystal**)
(**crystal polymorphism** of nateglinide)

IT Cooling
Drying
Precipitation (chemical)
(in producing the **crystal polymorphism** of nateglinide)

IT Mixing
(stirring; in producing the **crystal polymorphism** of nateglinide)

IT **105816-04-4**, Nateglinide
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)
(**crystal polymorphism** of nateglinide)

IT 7732-18-5, Water, uses 9004-65-3, Hydroxypropylmethylcellulose
RL: NUU (Other use, unclassified); USES (Uses)
(nonsolvent; in the **crystal polymorphism** of nateglinide)

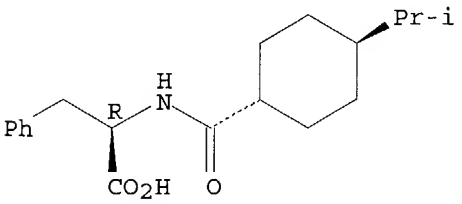
IT 64-17-5, Ethanol, uses 108-88-3, Toluene, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; in the **crystal polymorphism** of nateglinide)

IT **105816-04-4**, Nateglinide
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)
(**crystal polymorphism** of nateglinide)

RN 105816-04-4 CAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

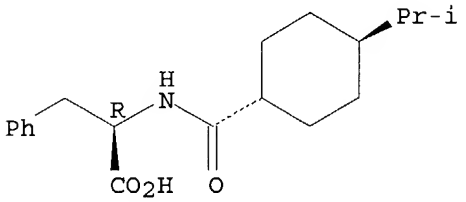
L11 ANSWER 6 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:762699 CAPLUS

DOCUMENT NUMBER: 140:64875
TITLE: Study of nateglinide **polymorphism**
AUTHOR(S): Li, Gang; Xu, Qunwei; Yao, Jie; Su, Guoqiang; Wang, Fang
CORPORATE SOURCE: Chemistry and Physics Central- laboratory, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China
SOURCE: Huagong Shikan (2002), 16(7), 17-18
CODEN: HUSHFT; ISSN: 1002-154X
PUBLISHER: Huagong Shikan Zazhishe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The **crystal** structure of nateglinide called an S form determined by an **x-ray** powder diffraction method. The pattern, data, and **crystal** size were obtained. The m.p. was determined by DSC as 172.04°.

CC 63-5 (Pharmaceuticals)
ST nateglinide **polymorphism crystal** structure
IT **Polymorphism** (**crystal**)
(nateglinide **polymorphism**)
IT **Crystal** structure
(of nateglinide **polymorph**)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nateglinide **polymorphism**)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nateglinide **polymorphism**)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:697592 CAPLUS
DOCUMENT NUMBER: 140:187130
TITLE: Study on stability of nateglinide **polymorphism**
AUTHOR(S): Li, Gang; Xu, Qun Wei; Mo, Xiang Yin; Chen, Jia Ying; Su, Guo Qiang
CORPORATE SOURCE: Chemistry and Physics Centralaboratory, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China
SOURCE: Chinese Chemical Letters (2003), 14(7), 730-733
CODEN: CCLEE7; ISSN: 1001-8417
PUBLISHER: Chinese Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

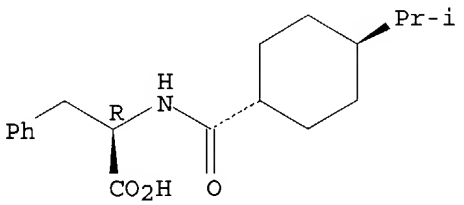
AB The stability of three forms of nateglinide, especially, S-form and H-form, was determined The S-form was a new **crystal** structure of nateglinide.

NPA

Three forms of nateglinide were treated under different conditions such as in various temps., humidity, light, etc. Anal. of their **crystal** structures was performed by **x-ray** powder diffraction and their particle shapes were observed with scanning electron microscope. The results indicated that the stability of S-form of nateglinide is the best among the three forms and their particle shapes are quite different. The S-form is the sheet structure of layer upon layer, H-form looks like a hank of silk lines and the B-form is of clubbed shape.

CC 63-5 (Pharmaceuticals)
ST nateglinide **polymorph** stability
IT **Crystal** structure
(of nateglinide and stability of **polymorphs**)
IT **Polymorphism** (**crystal**)
Thermal stability
(stability of nateglinide **polymorphs**)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stability of nateglinide **polymorphs**)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stability of nateglinide **polymorphs**)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



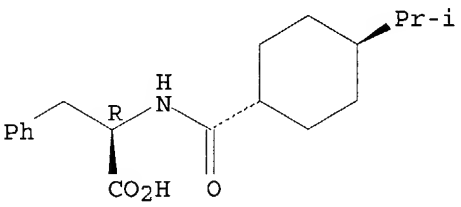
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:686087 CAPLUS
DOCUMENT NUMBER: 140:292376
TITLE: Study on the **crystal** types of nateglinide
AUTHOR(S): Sun, Piaoyang; Gou, Shaohua; Ma, Yonglin
CORPORATE SOURCE: State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing, 210093, Peop. Rep. China
SOURCE: Huaxue Yanjiu Yu Yingyong (2002), 14(4), 457-458, C3
CODEN: HYYIFM; ISSN: 1004-1656
PUBLISHER: Huaxue Yanjiu Yu Yingyong Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB N-(trans-4-methylethylcyclohexylcarbonyl)-D-phenylalanine, nateglinide, is an effective drug to decrease blood sugar, which is under clin. trials in China. This compound has been reported to have two **crystal** types, one of which is more suitable to prepare the drug. The nateglide with different **crystal** types was prepared Their m.ps., TGA-DTA and DSC spectral data, LR and **X-ray** powder diffraction spectra of all samples were studied with different **crystal** types. A new

crystal type that has not been reported in the literature was discovered. The method for controlling the **crystal** type was also presented.

CC 63-5 (Pharmaceuticals)
ST nateglide **polymorphism** antidiabetic
IT Antidiabetic agents
Crystal morphology
Crystal structure
Human
Polymorphism (**crystal**)
(**polymorphism** of nateglinide)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**polymorphism**; **polymorphism** of nateglinide)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**polymorphism**; **polymorphism** of nateglinide)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:221492 CAPLUS
DOCUMENT NUMBER: 138:243310
TITLE: Novel stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and process of preparation
INVENTOR(S): Shah, Vrajesh; Hitkari, Anurag; Deo, Keshav; Rengaraju, Srinivasan
PATENT ASSIGNEE(S): Alembic Limited, India
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

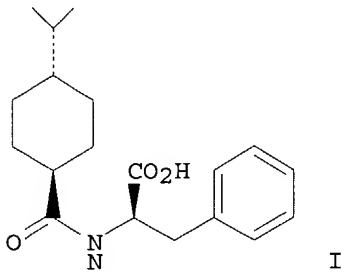
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003022251	A1	20030320	WO 2001-IB2080	20011105

W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, ES, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PH, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

NPA

BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: IN 2001-MU871 A 20010912
IN 2001-MU872 A 20010912

GI



I

AB A stable **crystal** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (I) may be produced by **crystallization** of I with a solvent at 25 - 38 °C and forming **crystals** in the solvent. The **crystal** form may be formed by recrystn. out of solution The **crystal** form obtained in this way have different m.p., infra red spectrum and **X-ray** diffraction patterns from previously known forms "B-type" and "H-Type" of the compound

IC ICM A61K009-14
ICS A61K009-16; C07C229-00

CC 63-6 (Pharmaceuticals)

ST phenylalanine isopropylcyclohexylcarbonyl **crystal** form

IT **Crystal** structure
(of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

IT **Crystal** morphology
(stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

IT **105816-04-4**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

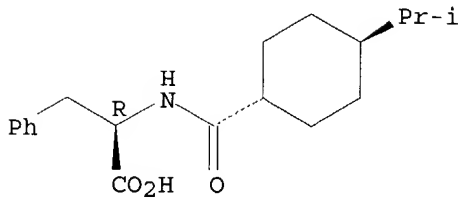
IT 68-12-2, Dmf, processes 75-05-8, Acetonitrile, processes 127-19-5, Dimethylacetamide
RL: PEP (Physical, engineering or chemical process); PYP (Physical process); PROC (Process)
(stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

IT **105816-04-4**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(stable **crystal** form of N-trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine)

RN 105816-04-4 CAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

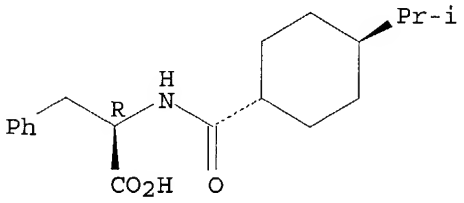
L11 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:146027 CAPLUS
DOCUMENT NUMBER: 139:235199
TITLE: Study on stability of nateglinide **polymorphism**
AUTHOR(S): Li, Gang; Xu, Qun-Wei; Mo, Xiang-Yin; Chen, Jia-Ying; Su, Guo-Qiang
CORPORATE SOURCE: Testing & Analysis Center, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China
SOURCE: Huaxue Xuebao (2003), 61(2), 291-294
CODEN: HHHPA4; ISSN: 0567-7351
PUBLISHER: Kexue Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

N1-A

AB A study has been made on the stability of three forms of nateglinide treated in different conditions, such as temperature, humidity, irradiation and so on. Anal. of the **crystal** structure was performed by **x-ray** powder diffraction. Their particle shapes were observed in scan electron microscope. The results show that the stability of S-form of nateglinide is the best among the three forms.

CC 63-5 (Pharmaceuticals)
ST nateglinide **polymorphism**
IT **Polymorphism** (**crystal**)
X-ray diffraction
(stability of nateglinide **polymorphism**)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stability of nateglinide **polymorphism**)
IT **105816-04-4**, Nateglinide
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stability of nateglinide **polymorphism**)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

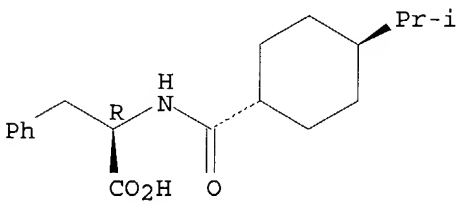


L11 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:62632 CAPLUS
DOCUMENT NUMBER: 138:73015
TITLE: Synthesis process for trans-4-isopropylcyclohexanecarboxylic acid
INVENTOR(S): Gu, Lianquan; An, Linkun; Ma, Lin; Guo, Xindong; Huang, Zhishu
PATENT ASSIGNEE(S): Zhongshan Univ., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 6 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1319583	A	20011031	CN 2001-107459	20010116

PRIORITY APPLN. INFO.: CN 2001-107459 20010116
OTHER SOURCE(S): CASREACT 138:73015
AB The process comprises hydrogenating cumic acid in acetic acid in the presence of PtO2, recovering solvent, treating with 10-35% inorg. base (such as Ba(OH)2, Mg(OH)2, KOH, or NaOH) solution at 50-150° for 10-20 h, neutralizing with HCl to pH 2, **crystallizing**, filtering, and recrystg. in methanol.
IC ICM C07C061-08
ICS C07C051-36
CC 24-5 (Alicyclic Compounds)
IT **105816-04-4P**, Nateglinide
RL: PNU (Preparation, unclassified); PREP (Preparation)
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)
IT **105816-04-4P**, Nateglinide
RL: PNU (Preparation, unclassified); PREP (Preparation)
(synthesis of trans-4-isopropylcyclohexanecarboxylic acid as intermediate for nateglinide)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



=> => d .ca l11 hitstr 12-25

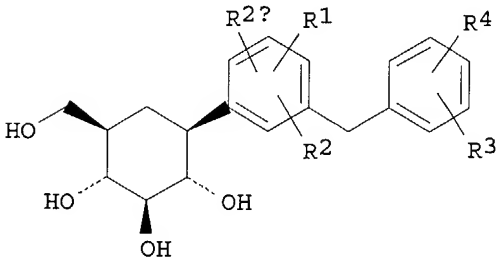
L11 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:813874 CAPLUS
DOCUMENT NUMBER: 137:311199

TITLE: Amino acid complexes of C-aryl glucosides for treatment of diabetes
INVENTOR(S): Gougoutas, Jack Z.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002083066	A2	20021024	WO 2002-US11066	20020408
WO 2002083066	A3	20030306		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003064935	A1	20030403	US 2002-117914	20020408
EP 1385856	A2	20040204	EP 2002-723801	20020408
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2001-283097P P 20010411
WO 2002-US11066 W 20020408

OTHER SOURCE(S): MARPAT 137:311199
GI



I

AB **Crystalline** complexes are obtained from 1:1 or 2:1 mixts. of either the (D) or (L) enantiomer of natural amino acids and compds. of formula I [R1, R2, R2a = H, OH, OR5, alkyl, OCHF2, OCF3, SR5a, halogen; R3, R4 = H, OH, OR5b, alkyl, cycloalkyl, CF3, OCHF2, OCF3, halogen, CONR6R6a, CO2R5c, CO2H, COR6b, CH(OH)R6c, CH(OR5d)R6d, CN, NHCOR5e, NHSO2R5f, NHSO2-aryl, SR5g, SOR5h, SO2R5i, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms (N, O, S, SO, and/or SO2), or R3 and R4 together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring; R5, R5a-R5i are independently alkyl; R6, R6a-R6d are independently H, alkyl, aryl, alkylaryl or cycloalkyl, or NR6R6a form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring]. A method is also provided for

treating diabetes and related diseases employing an SGLT2 (sodium dependent glucose transporters found in the intestine and kidney) inhibiting amount of the above complex alone or in combination with another antidiabetic agent or other therapeutic agent. Thus, I (R1 = 4-Me, R4 = 4-OCHF2, R2, R2a, R3 = H) was prepared by a multistep procedure starting from o-toluic acid, anisole, 2,3,4,6-tetra-O-benzyl-β-D-glucolactone, and CHF2Cl and treated with L-phenylalanine to form the **crystalline** 1:1 complex.

IC ICM A61K

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 33, 63, 75

ST **crystal** structure amino acid complex aryl glucoside; amino acid complex aryl glucoside prepn antidiabetic

IT Antidiabetic agents
Antiobesity agents
Atherosclerosis
Crystal structure
Diabetes mellitus
Human
Hyperglycemia
Hypertension
Hypertriglyceridemia
Hypolipemic agents
Obesity
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

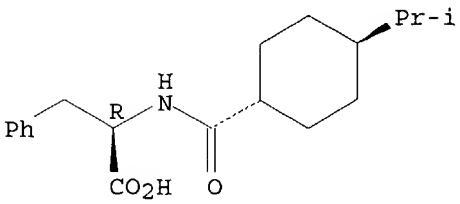
IT 51-64-9, Dexamphetamine 94-20-2, Chlorpropamide 122-09-8, Phentermine 637-07-0, Clofibrate 657-24-9, Metformin 9004-10-8, Insulin, biological studies 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 21187-98-4, Gliclazide 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 29094-61-9, Glipizide 49562-28-9, Fenofibrate 56180-94-0, Acarbose 72432-03-2, Miglitol 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 97322-87-7, Troglitazone **105816-04-4**, Nateglinide 106650-56-0, Sibutramine 111025-46-8, Pioglitazone 122320-73-4, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1, Repaglinide 141750-63-2, Nisvastatin 141758-74-9, AC2993 144288-97-1, TS 962 145599-86-6, Cerivastatin 147511-69-1, Pitavastatin 152755-31-2, LY295427 159183-92-3, L750355 161600-01-7, Isaglitazone 166518-60-1, Avasimibe 170861-63-9, JTT-501 176435-10-2, LY315902 178759-95-0, MD 700 196808-45-4 199113-98-9, NN-2344 199914-96-0, YM-440 213252-19-8, KRP297 244081-42-3, AJ9677 287714-41-4, Rosuvastatin 335149-08-1, L895645 335149-14-9, R-119702 335149-15-0, KAD1129 335149-17-2, ARHO39242 335149-19-4, GW-409544 335149-23-0, NVPDPP-728A 335149-24-1, ATL-962 335149-25-2, CP331648 416839-88-8, Axokine 430433-17-3, Glipyride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

IT **105816-04-4**, Nateglinide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of amino acid/C-aryl glucoside complexes for treatment of diabetes and related diseases)

RN 105816-04-4 CAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:811385 CAPLUS
DOCUMENT NUMBER: 139:12440
TITLE: Identification of nateglinide and its **crystal** forms in nateglinide tablets using IR Spectra subtraction techniques
AUTHOR(S): Lin, Kejiang; Chen, Wei; Tang, Weiguo; You, Qidong
CORPORATE SOURCE: Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing, 21009, Peop. Rep. China
SOURCE: Zhongguo Yaoke Daxue Xuebao (2002), 33(2), 124-126
CODEN: ZHYXE9; ISSN: 1000-5048
PUBLISHER: Zhongguo Yaoke Daxue
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The innovational identification method of IR (eliminated method) for detection of the **crystal** form of nateglinide in prepns. was presented. The IR spectrum by spectra subtraction techniques was obtained by subtracting IR spectrum after adding small volume of solvent to eliminate nateglinide from the spectrum of nateglinide tablets' KBr disk to identify the **crystal** form of nateglinide. The method (eliminated method) was useful in identification of the nateglinide **crystal** form in prepns.

CC 64-3 (Pharmaceutical Analysis)
Section cross-reference(s): 63

ST nateglinide tablet **crystal** form IR spectra

IT **Crystal** morphology
IR spectra
(identification of nateglinide and its **crystal** forms in nateglinide tablets using IR spectra subtraction techniques)

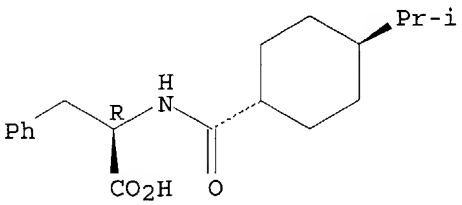
IT Drug delivery systems
(tablets; identification of nateglinide and its **crystal** forms in nateglinide tablets using IR spectra subtraction techniques)

IT **105816-04-4**, Nateglinide
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(identification of nateglinide and its **crystal** forms in nateglinide tablets using IR spectra subtraction techniques)

IT **105816-04-4**, Nateglinide
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(identification of nateglinide and its **crystal** forms in nateglinide tablets using IR spectra subtraction techniques)

RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:609152 CAPLUS
DOCUMENT NUMBER: 138:254901
TITLE: a new synthesis method of nateglinide as antidiabetic drug
AUTHOR(S): Wang, Dun; Liang, Yiheng; Gong, Ping; Zhao, Yanfang
CORPORATE SOURCE: School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, 110016, Peop. Rep. China
SOURCE: Zhongguo Yaowu Huaxue Zazhi (2002), 12(2), 94-96
CODEN: ZYHZEF; ISSN: 1005-0108
PUBLISHER: Zhongguo Yaowu Huaxue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 138:254901

AB A new antidiabetic drug-nateglinide was synthesized from isopropylbenzene by Friedel-Crafts reaction, chloroform reaction, catalytic hydrogenation to obtain trans-4-isopropylhexanecarboxylic acid, acylation of D-phenylalanine Et ester, hydrolysis to obtain nateglinide, B-type **crystal**, and **crystal**-conversion. The total yield was 9.8%.

CC 25-17 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 63

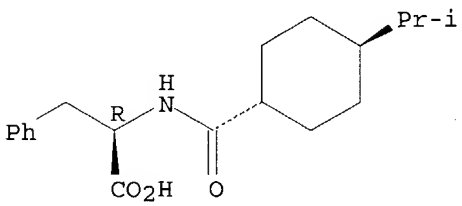
IT **Crystal** structure types
(type B; of nateglinide as antidiabetic drug)

IT **105816-04-4P**, Nateglinide
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of nateglinide as antidiabetic drug)

IT **105816-04-4P**, Nateglinide
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of nateglinide as antidiabetic drug)

RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:391524 CAPLUS
DOCUMENT NUMBER: 136:374894
TITLE: Nateglinide-containing hydrophilic drug preparations
INVENTOR(S): Ninomiya, Nobutaka; Makino, Chisato; Yabuki, Akira
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002040010	A1	20020523	WO 2001-JP9292	20011023
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001096000	A5	20020527	AU 2001-96000	20011023
BR 2001014897	A	20030812	BR 2001-14897	20011023
EP 1334721	A1	20030813	EP 2001-976818	20011023
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004029968	A1	20040212	US 2003-420886	20030423

PRIORITY APPLN. INFO.: JP 2000-324374 A 20001024
WO 2001-JP9292 W 20011023

AB Hydrophilic drug prepns. contain nateglinide B **crystals** useful as a hypoglycemic agent as the active ingredient which comprises a hydrophilic substance selected from the group consisting of hydrophilic polymers, surfactants, sugars, sugar alcs. and salts, and thus have a contact angle of the preparation surface to water of 111° or less. These prepns., which are rapid release prepns. having high elution properties, can be easily produced.

IC ICM A61K031-198
ICS A61K009-20; A61K009-28; A61K047-10; A61K047-26; A61K047-38; A61P003-10

CC 63-6 (Pharmaceuticals)

IT **Crystals**
(hypoglycemic hydrophilic drug prepns. containing nateglinide)

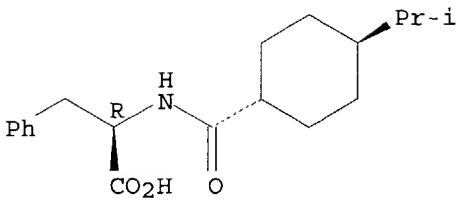
IT **105816-04-4**, Nateglinide
RL: BCP (Biochemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(hypoglycemic hydrophilic drug prepns. containing)

IT **105816-04-4**, Nateglinide
RL: BCP (Biochemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(hypoglycemic hydrophilic drug prepns. containing)

RN 105816-04-4 CAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:332157 CAPLUS
DOCUMENT NUMBER: 136:340998
TITLE: Process for producing B-form nateglinide **crystals**
INVENTOR(S): Sumikawa, Michito; Maruo, Makoto; Miyazaki, Kazuo; Nishina, Shigehiro; Matsuzawa, Yukiko
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034713	A1	20020502	WO 2001-JP9293	20011023
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001096001	A5	20020506	AU 2001-96001	20011023
EP 1334964	A1	20030813	EP 2001-976819	20011023
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001014846	A	20040225	BR 2001-14846	20011023
US 2003229249	A1	20031211	US 2003-421888	20030424

PRIORITY APPLN. INFO.: JP 2000-324375 A 20001024
WO 2001-JP9293 W 20011023

AB A process for producing B-form nateglinide **crystals** containing substantially no H-form **crystals** comprises the steps of drying wet **crystals** of a nateglinide solvate at a low temperature until the solvent disappears and then causing them to undergo a **crystal** transition. Nateglinide is a known antidiabetic. By this process, B-form nateglinide **crystals** can be produced on an industrial scale.

IC ICM C07C233-63
ICS C07C227-42

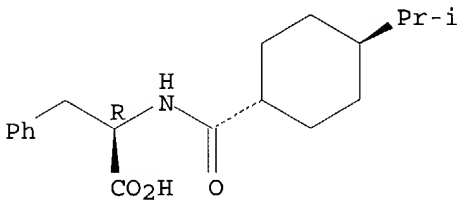
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 75

ST B form nateglinide **crystal** prepn antidiabetic

IT **Crystallization**
(**crystallization** of nateglinide)

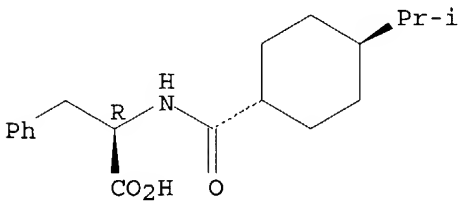
IT Differential scanning calorimetry
(industrial process for producing B-form nateglinide **crystals**
)
IT **105816-04-4P**, Nateglinide
RL: PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(industrial process for producing B-form nateglinide **crystals**
)
IT **173653-89-9**
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(industrial process for producing B-form nateglinide **crystals**
)
IT **105816-04-4P**, Nateglinide
RL: PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(industrial process for producing B-form nateglinide **crystals**
)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **173653-89-9**
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(industrial process for producing B-form nateglinide **crystals**
)
RN 173653-89-9 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, hydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:332027 CAPLUS
DOCUMENT NUMBER: 136:330583
TITLE: Nateglinide-containing preparations
INVENTOR(S): Ninomiya, Nobutaka; Makino, Chisato; Yabuki, Akira
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034254	A1	20020502	WO 2001-JP9291	20011023
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001095999	A5	20020506	AU 2001-95999	20011023
BR 2001014896	A	20030812	BR 2001-14896	20011023
EP 1334720	A1	20030813	EP 2001-976817	20011023
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004014815	A1	20040122	US 2003-421898	20030424

PRIORITY APPLN. INFO.: JP 2000-324373 A 20001024
WO 2001-JP9291 W 20011023

AB Disclosed are nateglinide-containing prepns. containing which are quick release prepns. useful as drugs for diabetes, wherein the nateglinide is in the amorphous state. The drug prepns. comprise hydrophilic substrates as carriers. **Crystalline** nateglinide 4 g and PVP 32 g were dissolved in ethanol and vacuum dried to give solid dispersions containing amorphous nateglinide.

IC ICM A61K031-198
ICS A61K009-06; A61K009-16; A61K009-20; A61K009-48; A61K047-10; A61K047-32; A61K047-34; A61K047-38; A61P003-10

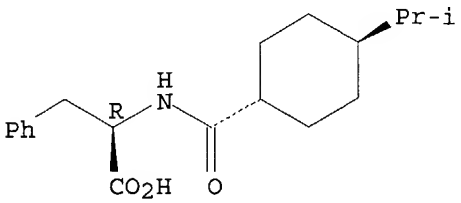
CC 63-6 (Pharmaceuticals)

IT 50-70-4, Sorbitol, biological studies 69-65-8, Mannitol 87-99-0, Xylitol 9002-89-5, Polyvinyl alcohol 9003-01-4, Polyacrylic acid 9004-64-2, Hydroxypropyl cellulose 9004-67-5, Methyl cellulose 9005-65-6, Polysorbate 80 25322-68-3, Polyethylene glycol 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6, Polylactic acid **105816-04-4**, Nateglinide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antidiabetic solid prepns. containing amorphous nateglinide and hydrophilic carriers)

IT **105816-04-4**, Nateglinide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antidiabetic solid prepns. containing amorphous nateglinide and hydrophilic carriers)

RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:314896 CAPLUS
DOCUMENT NUMBER: 136:325825
TITLE: Process for producing nateglinide **crystals**
INVENTOR(S): Takahashi, Daisuke; Nishi, Seiichi; Takahashi, Satoji
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032854	A1	20020425	WO 2001-JP9069	20011016
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001094265	A5	20020429	AU 2001-94265	20011016
EP 1334963	A1	20030813	EP 2001-974875	20011016
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001014729	A	20031014	BR 2001-14729	20011016
US 2004030182	A1	20040212	US 2003-418105	20030418

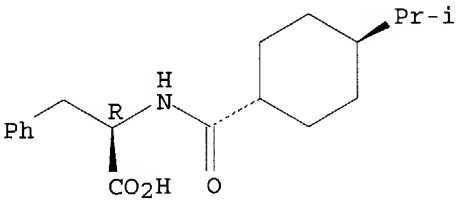
PRIORITY APPLN. INFO.: JP 2000-317604 A 20001018
WO 2001-JP9069 W 20011016

AB A process for producing nateglinide **crystals** comprises reacting trans-4-isopropylcyclohexylcarbonyl chloride with D-phenylalanine in a mixed solvent consisting of a ketone solvent and water in the presence of an alkali to obtain a reaction mixture containing nateglinide, adding an acid to the reaction mixture to make it acidic, and regulating (a) the temperature to 58° to 72° and (b) and the ketone solvent concentration to > 8 weight% and < 22 weight%, to conduct **crystallization** Nateglinide is a known antidiabetic. The process is an industrially advantageous method for **crystallizing** nateglinide.

IC ICM C07C231-24
ICS C07C231-02; C07C233-63

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 75
ST nateglinide **crystal** prepn antidiabetic
IT **Crystal** structure
(**crystal** structure of nateglinide)
IT **Crystallization**
(process for producing nateglinide **crystals**)
IT Alkali metal hydroxides
RL: RGT (Reagent); RACT (Reactant or reagent)
(process for producing nateglinide **crystals**)
IT Ketones, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvents; process for producing nateglinide **crystals**)
IT **105816-04-4P**, Nateglinide
RL: IMF (Industrial manufacture); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for producing nateglinide **crystals**)
IT 673-06-3, D-Phenylalanine 84855-54-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for producing nateglinide **crystals**)
IT 1310-58-3, Potassium hydroxide, reactions 7647-01-0, Hydrochloric acid, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(process for producing nateglinide **crystals**)
IT 67-64-1, Acetone, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; process for producing nateglinide **crystals**)
IT **105816-04-4P**, Nateglinide
RL: IMF (Industrial manufacture); PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(process for producing nateglinide **crystals**)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 19 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:234892 CAPLUS
DOCUMENT NUMBER: 137:39555
TITLE: Detection of **crystal polymorphs** of nateglinide by DSC
AUTHOR(S): Lin, Kejiang; Chen, Wei; You, Qidong
CORPORATE SOURCE: China Pharmaceutical University, Nanjing, 210009, Peop. Rep. China
SOURCE: Yaoxue Xuebao (2002), 37(1), 46-49

CODEN: YHHPAL; ISSN: 0513-4870
PUBLISHER: Yaoxue Xuebao Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The differential scanning calorimetric (DSC) methodol. for controlling the **crystal**-type B form of nateglinide was presented. Pure fine powder of **crystal**-type B and H of nateglinide dried with P2O5 as desiccant at 80° in vacuum for 4 h was measured dQ/dT by DSC at heating rate of 10° min-1 and temperature between 100° and 200° to calculate the enthalpy ΔHB and ΔHH. Uniform mixts. of **crystal**-type B and H of dried fine powder of nateglinide in different proportions were accurately weighed. The enthalpy of the mixts. was measured by DSC as above to calculate the enthalpy (ΠΔH). Using B% as X, ΠΔH as parameters, the regression equation was obtained. Based on this equation, the unknown composition of mixed **crystal** was evaluated by yδH values. The method was used to control the limitation of **crystal**-type B of nateglinide by the HδH value of mixture of known composition as reference The results measured from different labs. showed that the repeatability was 0.61% and recoveries were 86.2-127% when the amount of **crystal**-type B was between 0-15%. This method can be used to evaluate the **crystal**-type B composition of nateglinide.

CC 75-7 (Crystallography and Liquid Crystals)

ST nateglinide **crystal polymorph** control

IT **Crystal** growth
Differential scanning calorimetry
(control of **polymorphism** during **crystal** growth of nateglinide detected by DSC)

IT **Polymorphism** (**crystal**)
(detection of **crystal polymorphs** of nateglinide by DSC)

IT Enthalpy
(of **polymorphism** of nateglinide **crystals**)

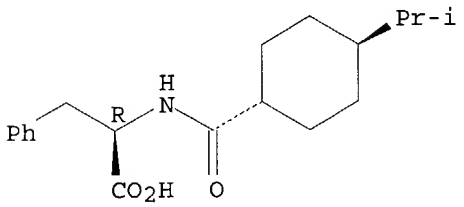
IT **105816-04-4**, Nateglinide
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)
(detection of **crystal polymorphs** of nateglinide by DSC)

IT **105816-04-4**, Nateglinide
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); PROC (Process)
(detection of **crystal polymorphs** of nateglinide by DSC)

RN 105816-04-4 CAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

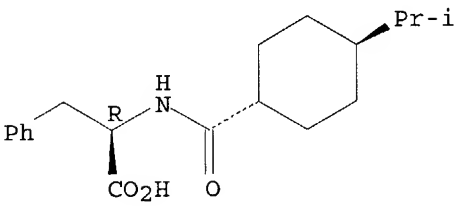
Absolute stereochemistry. Rotation (-).



L11 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:130037 CAPLUS
DOCUMENT NUMBER: 137:325603
TITLE: Synthesis of Nateglinide
AUTHOR(S): Zhu, Xue-yan; Peng, Ka; Wang, Xiao-qin; Yang, Li-ping
CORPORATE SOURCE: Dep. Chem., East China Normal Univ., Shanghai, 200062, Peop. Rep. China
SOURCE: Hecheng Huaxue (2001), 9(6), 537-540
CODEN: HEHUE2; ISSN: 1005-1511
PUBLISHER: Hecheng Huaxue Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 137:325603
AB Title compound, a new antidiabetes medicine, was synthesized from iso-propylbenzene in seven steps, giving the product with overall yield 22%.
CC 34-2 (Amino Acids, Peptides, and Proteins)
IT **105816-04-4DP**, Nateglinide, B **crystal** type
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and **crystalline** forms of)
IT **105816-04-4DP**, H **crystal** type
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of Nateglinide)
IT **105816-04-4DP**, Nateglinide, B **crystal** type
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and **crystalline** forms of)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of Nateglinide

L11 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:844448 CAPLUS
DOCUMENT NUMBER: 136:159110
TITLE: A new **crystal** structure in nateglinide found by **X-ray** powder diffraction
AUTHOR(S): Li, Gang; Su, Guo-qiang; Xu, Qun-wei
CORPORATE SOURCE: Center for Analysis & Measurement, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China
SOURCE: Yaowu Fenxi Zazhi (2001), 21(5), 342-344
CODEN: YFZADL; ISSN: 0254-1793
PUBLISHER: Yaowu Fenxi Zazhi Bianji Weiyuanhui
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB A new **crystal** structure being assigned as S-form was found in nateglinide. The **x-ray** pattern and data were given

and the m.p. was determined Phase anal. was carried out by **x-ray** powder diffraction; the m.ps. were determined by DSC. S-form nateglinide was different from the H or B **crystal** form. The m.p. was 172.04°. S-form nateglinide was a new **crystal** form. **X-ray** powder diffraction anal. was one of the most effective methods for phase structure characterization.

CC 75-8 (Crystallography and Liquid Crystals)
Section cross-reference(s): 1, 63

ST **crystal** structure nateglinide

IT **Crystal** structure
Molecular structure
(of nateglinide)

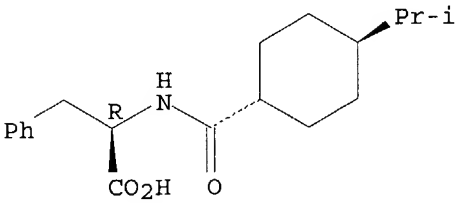
IT **105816-04-4**, Nateglinide
RL: PRP (Properties)
(**crystal** structure of)

IT **105816-04-4**, Nateglinide
RL: PRP (Properties)
(**crystal** structure of)

RN 105816-04-4 CAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 22 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:625224 CAPLUS

DOCUMENT NUMBER: 136:348527

TITLE: New **crystal** form of nateglinide

AUTHOR(S): Li, Gang; Su, Guoqiang; Xu, Qunwei; Zhu, Chongquan

CORPORATE SOURCE: Chemistry and Physics Central Laboratory, Nanjing Normal University, Nanjing, 210097, Peop. Rep. China

SOURCE: Yaoxue Xuebao (2001), 36(7), 532-534
CODEN: YHHPAL; ISSN: 0513-4870

PUBLISHER: Yaoxue Xuebao Bianjibu

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB The S form **crystals** of nateglinide [N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] were studied by XRD, IR, elemental anal., and differential scan calorimetry. The S-form nateglinide **crystal** was different from the H-form or B-form. The m.p. was 172.04°. The results showed that the S-form nateglinide was a new **crystal** form.

CC 75-8 (Crystallography and Liquid Crystals)
Section cross-reference(s): 1, 34, 63

ST nateglinide **X ray crystallog** study

IT **Crystal** structure
(**crystal** structure of nateglinide **crystals** (S-form))

IT **105816-04-4**, Nateglinide
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic

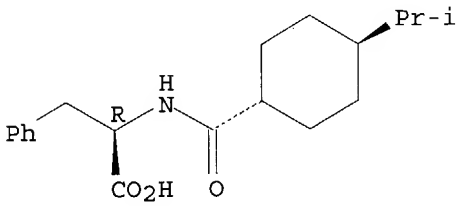
use); BIOL (Biological study); USES (Uses)
(new **crystal** form of nateglinide)

IT **105816-04-4**, Nateglinide
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new **crystal** form of nateglinide)

RN 105816-04-4 CAPLUS

CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 23 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:283772 CAPLUS
DOCUMENT NUMBER: 134:285620
TITLE: Method of treating metabolic disorders with nateglinide
INVENTOR(S): Gatlin, Marjorie Regan; Pongowski, Michele; Dunning, Beth
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001026639	A2	20010419	WO 2000-EP9816	20001006
WO 2001026639	A3	20020110		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1218015	A2	20020703	EP 2000-972695	20001006
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

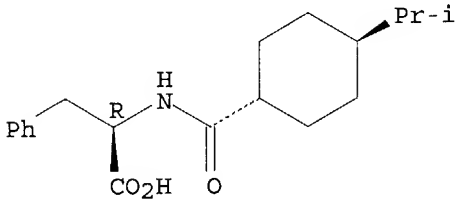
PRIORITY APPLN. INFO.: US 1999-415307 A 19991008
US 1999-415308 A 19991008
WO 2000-EP9816 W 20001006

AB The invention relates to a combination which comprises nateglinide and (a) an antidiabetic phenylacetic acid derivative or (b) acarbose for simultaneous, sep. or sequential use, in particular in the treatment of diseases, especially

metabolic disorders; to a method of prevention, delay of progression or treatment of metabolic disorders, more especially diabetes, or a disease or condition associated with diabetes, and to a method of improving the bodily appearance of a warm-blooded animal.

IC ICM A61K031-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2
IT **Crystal** morphology
(of nateglinide; treating metabolic disorders with nateglinide)
IT 103-82-2D, Phenylacetic acid, derivs. 657-24-9, Metformin 2295-31-0D, Thiazolidinedione, derivs. 9004-10-8, Insulin, biological studies 56180-94-0, Acarbose **105816-04-4**, Nateglinide 135062-02-1, Repaglinide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(treating metabolic disorders with nateglinide)
IT **105816-04-4**, Nateglinide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(treating metabolic disorders with nateglinide)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L11 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:964992 CAPLUS
DOCUMENT NUMBER: 124:155974
TITLE: **Crystals** of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine and methods for preparing them
INVENTOR(S): Sumikawa, Michito; Koguchi, Yoshihito; Ohgane, Takao; Irie, Yasuo; Takahashi, Satoji
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: U.S., 12 pp. Cont.-in-part of U.S. Ser. No. 166,144.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

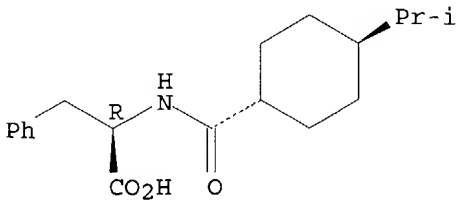
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5463116	A	19951031	US 1994-190460	19940202
US 5488150	A	19960130	US 1993-166144	19931214
CA 2114678	AA	19950802	CA 1994-2114678	19940201
CA 2114678	C	19990427		

PRIORITY APPLN. INFO.: JP 1991-189696 A 19910730
JP 1991-199453 A 19910808
US 1992-921224 B1 19920729
US 1993-166144 A2 19931214

AB Stable **crystals** of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine for pharmaceutical formulation may be produced by treating this compound with a solvent at a temperature of at least 10° and forming **crystals** in the solvent at a temperature of at least 10°. For example, **crystals** may be formed by **crystallization** out of solution, or may be formed from solid particles of the compound suspended in a solvent. **Crystals** formed in this way have different m.p., IR spectrum and **X-ray** diffraction patterns from previously known forms of the compound and have enhanced processability, e.g., stability to grinding.

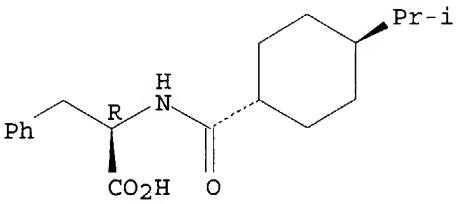
IC ICM C07C229-00
NCL 562450000
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 75
ST isopropylcyclohexylcarbonyl phenylalanine **crystn** grinding
IT **Crystallization**
Solvent effect
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)
IT Size reduction
(grinding, **crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)
IT 64-17-5, Ethanol, uses 67-56-1, Methanol, uses 67-64-1, Acetone, uses 75-05-8, Acetonitrile, uses 7732-18-5, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)
IT **105816-04-4**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)
IT **173653-89-9**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)
IT **105816-04-4**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **173653-89-9**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**crystallization** of (isopropylcyclohexylcarbonyl)phenylalanine for enhanced stability to grinding)
RN 173653-89-9 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]-, hydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



●x H_2O

L11 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:261002 CAPLUS
DOCUMENT NUMBER: 118:261002
TITLE: Stable **crystals** of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine
INVENTOR(S): Sumikawa, Michito; Koguchi, Yoshihito; Ohgane, Takao; Irie, Yasuo; Takahashi, Satoji
PATENT ASSIGNEE(S): Ajinomoto Co., Inc., Japan
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 526171	A2	19930203	EP 1992-306895	19920729
EP 526171	A3	19930505		
EP 526171	B1	19970305		
R: AT, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE				
JP 05208943	A2	19930820	JP 1992-202686	19920729
JP 2508949	B2	19960619		
AT 149483	E	19970315	AT 1992-306895	19920729
ES 2100291	T3	19970616	ES 1992-306895	19920729
CA 2114678	AA	19950802	CA 1994-2114678	19940201
CA 2114678	C	19990427		

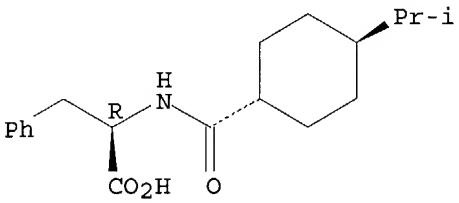
PRIORITY APPLN. INFO.: JP 1991-189696 A 19910730
JP 1991-199453 A 19910808

AB Stable H-type **crystals** of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (I) are obtained by treating I with a solvent, at >10°. A solution of 5 g I in 20 mL acetone was added to a stirred mixture of 40 mL acetone and 60 mL water, at 25°

to precipitate H-type **crystals.** The **crystals** have different m.p., IR spectrum and **x-ray** diffraction patterns from known forms of I and are not converted to other forms when ground.

IC ICM C07C233-63
ICS A61K031-195
CC 63-5 (Pharmaceuticals)
ST phenylalanine deriv drug stable **crystal**
IT **105816-04-4P**
RL: PREP (Preparation)
(**crystals**, stable, preparation of)
IT **105816-04-4P**
RL: PREP (Preparation)
(**crystals**, stable, preparation of)
RN 105816-04-4 CAPLUS
CN D-Phenylalanine, N-[[trans-4-(1-methylethyl)cyclohexyl]carbonyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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=> fil wpids
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http://www.thomsonscientific.com/litalert <<<

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=> d que l13
L12          90 SEA FILE=WPIDS ABB=ON  PLU=ON  NATEGLINIDE OR SENAGLINIDE OR
                STARLIX OR STARSIS OR FASTIC OR AY 4166 OR A 4166
L13          15 SEA FILE=WPIDS ABB=ON  PLU=ON  L12 AND CRYS?


=> d bib ab  l13 1-15

L13  ANSWER 1 OF 15  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
AN   2004-269196 [25]   WPIDS
DNC  C2004-104807
TI   New crystalline form of nateglinide useful to treat
     diabetes and to stimulate insulin secretion from pancreas.
DC   B05
IN   KADABOINA, R; POLAVARAPU, S; REGURI, B R
PA   (REDD-N) REDDY'S LAB LTD
CYC  105
PI   WO 2004020396   A1 20040311 (200425)* EN   29
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            LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
            PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC
            VN YU ZA ZM ZW
     US 2004077725   A1 20040422 (200428)
ADT  WO 2004020396 A1 WO 2003-US26880 20030827; US 2004077725 A1 US 2003-649380
     20030827
PRAI IN 2002-CH631        20020828
AB   WO2004020396 A UPAB: 20040525
     NOVELTY - Crystalline form X of nateglinide (I) is
     new.
          DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for
          (1) a composition (B) comprising nateglinide as a solid,
     where at least 80% by weight of the solid is (I); and
          (2) preparation of (I).
          ACTIVITY - Antidiabetic.
          MECHANISM OF ACTION - None given in the source material.
          USE - (I) is useful to treat diabetes and also stimulates the
     secretion of insulin from pancreas.
     Dwg.0/2

L13  ANSWER 2 OF 15  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
AN   2004-180282 [17]   WPIDS
CR   2004-108803 [11]
DNC  C2004-071244
TI   New crystalline polymorphic forms of nateglinide
     useful for lowering the blood sugar level.
DC   B05
IN   DOLITZKY, B; GOME, B; GOZLAN, Y; SHAPIOR, E; YAHALOMI, R
PA   (TEVA-N) TEVA PHARM IND LTD; (TEVA-N) TEVA PHARM USA INC
CYC  105
PI   WO 2004009532   A1 20040129 (200417)* EN  130
```

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC
VN YU ZA ZM ZW

ADT WO 2004009532 A1 WO 2003-US22375 20030718

PRAI US 2003-614266 20030703; US 2002-396904P 20020718;
US 2002-413622P 20020925; US 2002-414199P 20020926;
US 2002-423750P 20021105; US 2002-432093P 20021210;
US 2002-432962P 20021212; US 2003-442109P 20030123;
US 2003-449791P 20030224; US 2003-479016P 20030616

AB WO2004009532 A UPAB: 20040310
NOVELTY - 26 **Crystalline nateglinide** forms as characterized by XRPD patterns, DSC thermograms and FTIR spectra, fully described in the specification, are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the preparation of the **crystalline** forms of **nateglinide.**
ACTIVITY - Antidiabetic.
No test details for antidiabetic activity are given.
MECHANISM OF ACTION - None given.
USE - The pharmaceutical formulation comprising **crystalline nateglinide** form of A, C, D, F, G, I, J, K, M, N O, Q, T, V, Y, gamma, epsilon, theta or omega is useful to lower the blood sugar level (claimed).
ADVANTAGE - The new polymorphic forms of **nateglinide** provides a new opportunity to improve the performance characteristics of a pharmaceutical product.
Dwg.0/64

L13 ANSWER 3 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-108803 [11] WPIDS
CR 2004-180282 [17]
DNC C2004-044538
TI Preparation of trans-4-isopropylcyclohexane acid chloride as intermediate in preparing **nateglinide** comprises reaction between thionyl chloride and acid chloride in the presence of organic amide.
DC B05
IN DOLITZKY, B; GOZLAN, Y; SHAPIRO, E; YAHALOMI, R
PA (TEVA-N) TEVA PHARM IND LTD; (TEVA-N) TEVA PHARM USA INC
CYC 105
PI WO 2004005240 A1 20040115 (200411)* EN 31
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC
VN YU ZA ZM ZW

ADT WO 2004005240 A1 WO 2003-US21238 20030703

PRAI US 2003-479016P 20030616; US 2002-393495P 20020703;
US 2002-396904P 20020718; US 2002-413622P 20020925;
US 2002-414199P 20020926; US 2002-423750P 20021105;
US 2002-432093P 20021210; US 2002-432962P 20021212;
US 2003-442109P 20030123; US 2003-449791P 20030224

AB WO2004005240 A UPAB: 20040310
NOVELTY - Preparing trans-4-isopropylcyclohexane acid chloride comprises combining trans-4-isopropylcyclohexane carboxylic acid with thionyl chloride in the presence of a 1-6C organic amide to obtain

trans-4-isopropylcyclohexane acid chloride free of its corresponding cis isomer; and recovering the trans-4-isopropylcyclohexane acid chloride.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a process for preparing **nateglinide** by combining trans-4-isopropylcyclohexane carboxylic acid with thionyl chloride in the presence of a 1-6C organic amide to obtain trans-4-isopropylcyclohexane acid chloride free of its corresponding cis isomer; converting the acid chloride to **nateglinide**; and recovering the **nateglinide**

.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - For preparing trans-4-isopropylcyclohexane acid chloride as an intermediate in preparing **nateglinide** for the treatment of type II diabetes.

ADVANTAGE - The cis-isomer is not formed nor detected in amounts of less than 0.05% even at elevated temperature (60-80 deg. C) in the reaction between thionyl chloride and trans-isopropylcyclohexane carboxylic acid in the presence of an organic amide catalyst.

Dwg.0/3

L13 ANSWER 4 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-081844 [08] WPIDS
DNC C2004-033612
TI New **crystal** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine useful for lowering blood glucose level.
DC A96 B05
IN SUTTON, P A
PA (NOVS) NOVARTIS AG; (NOVS) NOVARTIS PHARMA GMBH
CYC 90
PI WO 2003087038 A1 20031023 (200408)* EN 5
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LT LU LV MA MD MK MN MX NI NO NZ OM PH PL PT RO RU SC SE SG SK TJ TM TN TR TT UA US UZ VC VN YU ZA ZW
AU 2003242520 A1 20031027 (200436)
ADT WO 2003087038 A1 WO 2003-EP3864 20030414; AU 2003242520 A1 AU 2003-242520 20030414
FDT AU 2003242520 A1 Based on WO 2003087038
PRAI US 2002-372625P 20020415
AB WO2003087038 A UPAB: 20040202

NOVELTY - A **crystal** form of N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine (**nateglinide**) having melting point of 108 deg. C, or its solvate is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the production of R'-type **crystal** form of **nateglinide** involving:

(a) dissolving **nateglinide** in any of its forms in a solvent (S1) in which **nateglinide** is readily soluble at an ambient temperature to form a solution;

(b) treating the solution with another solvent (S2) which is miscible with (S1) and in which **nateglinide** is poorly soluble to induce precipitation of R'-type **crystals** of **nateglinide**; and

(c) isolating and drying the precipitate **crystal** form of **nateglinide.**

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - For lowering blood glucose level in human.

ADVANTAGE - The **nateglinide** in any of its form, such as

hydrates, methanolates, ethanolates and acetonates can be used for the production of R'-type **crystal.**
Dwg.0/2

L13 ANSWER 5 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-853914 [79] WPIDS
DNC C2003-240851
TI New **crystalline nateglinide** forms A, M and P are antiglycemic agents and antidiabetic agents.
DC B05
IN KOGUCHI, Y; NAKAO, T; SUMIKAWA, M
PA (AJIN) AJINOMOTO CO INC
CYC 103
PI WO 2003087039 A1 20031023 (200379)* JA 17
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003236243 A1 20031027 (200436)
ADT WO 2003087039 A1 WO 2003-JP4686 20030414; AU 2003236243 A1 AU 2003-236243 20030414
FDT AU 2003236243 A1 Based on WO 2003087039
PRAI JP 2002-111963 20020415
AB WO2003087039 A UPAB: 20031208
NOVELTY - **Crystalline nateglinide** forms A, M and P are new.
DETAILED DESCRIPTION - **Crystalline nateglinide** of formula (I) forms A, M and P are new.
USE - **Nateglinide** is an antiglycemic agent and antidiabetic agent.
ADVANTAGE - Have improve stability and solubility.
Dwg.0/3

L13 ANSWER 6 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-748369 [70] WPIDS
DNC C2003-205231
TI New salt of **nateglinide** useful for treating, e.g. diabetes, cardiovascular or related diseases, e.g. hyperglycemia, hyperlipidaemia, obesity, diabetes retinopathy, diabetic neuropathy, glomerulosclerosis or stroke.
DC B05
IN DE LA CRUZ, M; PARKER, D J; SUTTON, P A; VIVILECCHIA, R V
PA (NOVS) NOVARTIS AG; (NOVS) NOVARTIS PHARMA GMBH
CYC 90
PI WO 2003076393 A1 20030918 (200370)* EN 23
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LT LU LV MA MD MK MN MX NI NO NZ OM PH PL PT RO RU SC SE SG SK TJ TM TN TR TT UA US UZ VC VN YU ZA ZW
AU 2003214112 A1 20030922 (200431)
ADT WO 2003076393 A1 WO 2003-EP2447 20030310; AU 2003214112 A1 AU 2003-214112 20030310
FDT AU 2003214112 A1 Based on WO 2003076393
PRAI US 2002-363178P 20020311
AB WO2003076393 A UPAB: 20031030

NOVELTY - A salt of **nateglinide** (I) having a melting point of 50-300 deg. C is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) A composition comprising (I); and

(2) A method for the treatment of diabetes, cardiovascular disease or related conditions, comprising administration of (I).

ACTIVITY - Antidiabetic; Antilipemic; Anorectic; Ophthalmological; Neuroprotective; Nephrotropic; Vasotropic; Antiulcer; Antiinflammatory; Cardiant; Hypotensive; Antianginal; Cerebroprotective; Dermatological; Antiarthritic; Osteopathic; Vasotropic; Cardiovascular-Gen.

Test details are described, but no results given.

MECHANISM OF ACTION - None given.

USE - (I) is used for treating diabetes, cardiovascular or related diseases, e.g. hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, obesity, diabetes retinopathy, macular degeneration, cataracts, diabetic neuropathy, glomerulosclerosis, erectile dysfunction, premenstrual syndrome, vascular restenosis, ulcerative colitis, coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, skin and connective tissue disorder, foot ulcerations, metabolic acidosis, arthritis, osteoporosis, polycystic ovary syndrome or impaired glucose tolerance (all claimed).

ADVANTAGE - The salt of **nateglinide** has a higher degree of dissociation in water, increased biological availability of the salts, salt hydrates, or salt anions in the case of solid dosage forms. For different relative humidities at room temperature, the salts shows (with the exception of potassium and a calcium salt) practically no water absorption or water loss over a wide range of humidities and for periods of few hours, e.g. four hours. The melting point of the salts will not be changed by storing under different relative humidities, except for the melting point of those salts that are hygroscopic or moderately hygroscopic. (I) has a water solubility of at least 0.18 (preferably at least 0.4, especially 40) mg/ml.

Dwg.0/0

L13 ANSWER 7 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-111806 [10] WPIDS
DNC C2003-028518
TI New **crystalline** complex between either (D) or (L) enantiomers of natural amino acids and amorphous C-aryl glucoside compounds useful for treating e.g. diabetes.
DC B03
IN GOUGOUTAS, J Z
PA (GOUG-I) GOUGOUTAS J Z; (BRIM) BRISTOL-MYERS SQUIBB CO
CYC 101
PI WO 2002083066 A2 20021024 (200310)* EN 80
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003064935 A1 20030403 (200325)
EP 1385856 A2 20040204 (200410) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
AU 2002254567 A1 20021028 (200433)
ADT WO 2002083066 A2 WO 2002-US11066 20020408; US 2003064935 A1 Provisional US 2001-283097P 20010411, US 2002-117914 20020408; EP 1385856 A2 EP 2002-723801 20020408, WO 2002-US11066 20020408; AU 2002254567 A1 AU

2002-254567 20020408
FDT EP 1385856 A2 Based on WO 2002083066; AU 2002254567 A1 Based on WO 2002083066
PRAI US 2001-283097P 20010411; US 2002-117914 20020408
AB WO 200283066 A UPAB: 20030211
NOVELTY - A **crystalline** complex between either (D) or (L) enantiomers of natural amino acid and amorphous C-aryl glucoside compound is new.

DETAILED DESCRIPTION - **Crystalline** complexes between either (D) or (L) enantiomers of natural amino acids and compound of formula (I) are new.

R1, R2 and R2a = H, OH, OR5, alkyl, -OCHF2, -OCF3, -SR5a or halo;

R3 and R4 = H, OH, OR5b, (cyclo)alkyl, CF3, -OCHF2, -OCF3, halogen, -CONR6R6a, -CO2R5c, -CO2H, -COR6b, -CH(OH)R6c, -CH(OR5d)R6d, -CN, -NHCOR5e, -NHSO2R5f, -NHSO2Aryl, -SR5g, -SOR5h, SO2R5i or 5 - 7-membered heterocycle (containing 1 - 4 heteroatoms of N, O, S, SO and/or SO2);

R3+R4 and NR6+R6a = annelated 5 - 7-membered carbocycle or heterocycle (both containing 1 - 4 heteroatoms of N, O, S, SO and/or SO2));

R5 and R5a - R5i = alkyl;

R6 and R6a - R6d = H, alkyl, (alkyl)aryl or cycloalkyl.

INDEPENDENT CLAIMS are included for the following:

(1) A pharmaceutical combination (A1) comprising complex of either the (D) or (L) enantiomer of natural amino acids with (I) and a component (G1) selected from an antidiabetic agent (G) other than an SGLT2 inhibitor, an agent for treating the complications of diabetes, an anti-obesity agent, an antihypertensive agent, an antiplatelet agent, an antiatherosclerotic agent and/or a lipid-lowering agent (preferably G); and

(2) Treating type II diabetes involving administering the complex of (I) alone or in combination with another antidiabetic agent, an agent for treating the complications of diabetes, an anti-obesity agent, an antihypertensive agent, an antiplatelet agent, an antiatherosclerotic agent and/or a hypolipidemic agent.

ACTIVITY - Antidiabetic; Ophthalmological; Neuroprotective; Vulnerary; Anorectic; Antiarteriosclerotic; Hypotensive; Nephrotropic.

MECHANISM OF ACTION - Inhibitors of sodium dependent glucose transporters.

USE - Compound (I) is used for treating or delaying the progression or onset of diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, delayed wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis or hypertension or for increasing high density lipoprotein levels and for treating type II diabetes (claimed).

ADVANTAGE - The complex normalizes the plasma glucose by enhancing the excretion of glucose in the urine, thus improves insulin sensitivity and delays the development of diabetic complications.

Dwg.0/0

L13 ANSWER 8 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-713487 [77] WPIDS
DNC C2002-202321
TI Combination used for treating e.g. hypertension, obesity, diabetic neuropathy and arthritis comprises **nateglinide** or repaglinide and additional antidiabetic compound e.g. insulin.
DC B02 B05
IN VILLHAUER, E B
PA (NOVS) NOVARTIS AG; (NOVS) NOVARTIS PHARMA GMBH; (NOVS) NOVARTIS-ERFINDUNGEN VERW GES MBH

CYC 88
PI WO 2002072146 A2 20020919 (200277)* EN 30
RW: AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE TR
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LT LU LV MA MD MK MN MX NO NZ OM PH PL PT RO RU SE SG SI SK TJ TM TN TR TT UA US UZ VN YU ZA ZW
EP 1385549 A2 20040204 (200410) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
AU 2002254940 A1 20020924 (200433)
ADT WO 2002072146 A2 WO 2002-EP2665 20020311; EP 1385549 A2 EP 2002-724221 20020311, WO 2002-EP2665 20020311; AU 2002254940 A1 AU 2002-254940 20020311
FDT EP 1385549 A2 Based on WO 2002072146; AU 2002254940 A1 Based on WO 2002072146
PRAI US 2001-275098P 20010312
AB WO 200272146 A UPAB: 20021129

NOVELTY - Combination comprises **nateglinide** or repaglinide, at least one additional antidiabetic compound and optionally at least one carrier.

DETAILED DESCRIPTION - Combination comprises **nateglinide** or repaglinide, at least one additional antidiabetic compound and optionally at least one carrier. The antidiabetic compound comprises insulin signaling pathway modulator, compounds influencing a dys-regulated hepatic glucose production, pyruvate dehydrogenase kinase (PDHK) inhibitor, inhibitors of gastric emptying, insulin, inhibitors of glycogen synthase kinase-3, retinoid X receptor (RXR) agonists, agonists of human beta -3 adrenergic receptor, agonists of uncoupling proteins (UCPs), non-glitazone type PPAR- gamma , dual PPAR- gamma /PPAAR- alpha agonists, antidiabetic vanadium containing compounds, incretin hormones, beta -cell imidazoline receptor antagonist, miglitol or alpha 2-adrenergic antagonists.

The active ingredients are contained in the free form or in the form of their salts.

An INDEPENDENT CLAIM is also included for a commercial package comprising the combination together with instructions for simultaneous, separate or sequential used in the prevention, delay of progression or treatment of metabolic disorders or for improving the bodily appearance.

ACTIVITY - Antidiabetic; Ophthalmological; Anorectic; Nephrotropic; Vasotropic; Gynecological; Antiinflammatory; Antiulcer; Cardiant; Hypotensive; Cerebroprotective; Dermatological; Antiarthritic; Osteopathic.

MECHANISM OF ACTION - Iinsulin signaling pathway modulator; Pyruvate dehydrogenase kinase inhibitor; Retinoid X receptor agonist; Glycogen synthase kinase-3 inhibitor; Human beta -3 adrenergic receptor; Uncoupling protein agonist; beta -cell imidazoline receptor antagonist; Miglitol antagonist; alpha 2-adrenergic antagonist; Non-glitazone type PPAR- gamma , dual PPAR- gamma /PPAAR- alpha agonist.

No biological tests or results are given in the source material.

USE - Used for the prevention, delay of progression or treatment of metabolic disorders and for cosmetic treatment to obtain body weight loss (all claimed). The combination is used for treating hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis, ulcerative colitis, coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, skin and connective tissue disorders, foot ulceration, metabolic acidosis, arthritis, osteoporosis and impaired glucose tolerance.

ADVANTAGE - The combination results in a beneficial, especially a synergistic, therapeutic effect. The combination also provides efficacy, a broader variety of therapeutic treatment and beneficial effects on diseases and conditions associated with diabetes, which includes less gain of weight, compared to a mono-therapy applying only one of the active ingredients of the combination.
Dwg.0/0

L13 ANSWER 9 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-507933 [54] WPIDS
DNC C2002-144389
TI Process for producing **nateglinide crystals** useful for treating diabetes involves reacting trans-4-isopropylcyclohexylcarbonyl chloride with D-phenylalanine in ketone and water in presence of alkali.
DC B05
IN NISHI, S; TAKAHASHI, D; TAKAHASHI, S
PA (AJIN) AJINOMOTO CO INC; (AJIN) AJINOMOTO KK
CYC 98
PI WO 2002032854 A1 20020425 (200254)* JA 15
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001094265 A 20020429 (200255)
EP 1334963 A1 20030813 (200355) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
BR 2001014729 A 20031014 (200374)
KR 2003059203 A 20030707 (200377)
US 2004030182 A1 20040212 (200412)
JP 2002536038 X 20040226 (200416)
MX 2003003484 A1 20030701 (200423)
CN 1481356 A 20040310 (200437)
ADT WO 2002032854 A1 WO 2001-JP9069 20011016; AU 2001094265 A AU 2001-94265 20011016; EP 1334963 A1 EP 2001-974875 20011016, WO 2001-JP9069 20011016; BR 2001014729 A BR 2001-14729 20011016, WO 2001-JP9069 20011016; KR 2003059203 A KR 2003-705388 20030417; US 2004030182 A1 Cont of WO 2001-JP9069 20011016, US 2003-418105 20030418; JP 2002536038 X WO 2001-JP9069 20011016, JP 2002-536038 20011016; MX 2003003484 A1 WO 2001-JP9069 20011016, MX 2003-3484 20030416; CN 1481356 A CN 2001-820658 20011016
FDT AU 2001094265 A Based on WO 2002032854; EP 1334963 A1 Based on WO 2002032854; BR 2001014729 A Based on WO 2002032854; JP 2002536038 X Based on WO 2002032854; MX 2003003484 A1 Based on WO 2002032854
PRAI JP 2000-317604 20001018
AB WO 200232854 A UPAB: 20020823
NOVELTY - A process for producing **nateglinide crystals** involves:

(i) reacting trans-4-isopropylcyclohexylcarabonyl chloride with D-phenylalanine in a mixed solvent, consisting of a ketone and water in the presence of an alkali; and

(ii) adding an acid to the resulting reaction mixture and subjected to **crystallization** while regulating the temperature and the ketone solvent concentration.

DETAILED DESCRIPTION - A process for producing **nateglinide crystals** involves:

(i) reacting trans-4-isopropylcyclohexylcarbonyl chloride with D-phenylalanine in a mixed solvent, consisting of a ketone and water in

the presence of an alkali; and
(ii) adding an acid, providing an acidic condition to the resulting reaction mixture, containing **nateglinide** and subjected to **crystallization** while regulating the temperature (between 58 - 72 deg. C) and the ketone solvent concentration (between 9 to up to but not including 22 wt%).
USE - For producing **nateglinide crystals**, which can be used as an oral medicine for treating diabetes.
ADVANTAGE - The process is efficient even on an industrial production scale.
Dwg.0/0

L13 ANSWER 10 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-500188 [53] WPIDS
DNC C2002-141632
TI Hydrophilic drug preparation comprises **nateglinide** B **crystals** and has contact angle to water surface of 111 degrees or less useful as an hypoglycemic agent.
DC A96 B05
IN MAKINO, C; NINOMIYA, N; YABUKI, A
PA (AJIN) AJINOMOTO CO INC; (AJIN) AJINOMOTO KK
CYC 98
PI WO 2002040010 A1 20020523 (200253)* JA 26
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001096000 A 20020527 (200261)
EP 1334721 A1 20030813 (200355) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2003042028 A 20030527 (200361)
BR 2001014897 A 20030812 (200367)
US 2004029968 A1 20040212 (200412)
JP 2002542384 X 20040603 (200436)
CN 1482904 A 20040317 (200437)
ADT WO 2002040010 A1 WO 2001-JP9292 20011023; AU 2001096000 A AU 2001-96000 20011023; EP 1334721 A1 EP 2001-976818 20011023, WO 2001-JP9292 20011023; KR 2003042028 A KR 2003-705635 20030423; BR 2001014897 A BR 2001-14897 20011023, WO 2001-JP9292 20011023; US 2004029968 A1 Cont of WO 2001-JP9292 20011023, US 2003-420886 20030423; JP 2002542384 X WO 2001-JP9292 20011023, JP 2002-542384 20011023; CN 1482904 A CN 2001-821218 20011023
FDT AU 2001096000 A Based on WO 2002040010; EP 1334721 A1 Based on WO 2002040010; BR 2001014897 A Based on WO 2002040010; JP 2002542384 X Based on WO 2002040010
PRAI JP 2000-324374 20001024
AB WO 200240010 A UPAB: 20020820
NOVELTY - Hydrophilic drug preparation comprises **nateglinide** B **crystals** and has a contact angle to the surface of water of 111 deg. or less.
ACTIVITY - Antidiabetic.
MECHANISM OF ACTION - None given.
USE - As a hydrophillic drug preparation for administering **nateglinide** B **crystals** useful as an hypoglycemic agent.
ADVANTAGE - Have quick release with high elution properties and are easily produced.
Dwg.0/0

L13 ANSWER 11 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-462521 [49] WPIDS
CR 1999-204733 [17]; 2000-170837 [15]; 2001-432562 [46]; 2001-522427 [57]; 2001-595790 [67]; 2002-082346 [11]; 2002-215543 [27]; 2002-215909 [27]; 2002-315576 [35]; 2002-328338 [36]; 2002-635742 [68]; 2002-666828 [71]; 2002-696871 [75]; 2003-015683 [01]; 2003-198106 [19]; 2003-238931 [23]; 2003-417948 [39]; 2003-627162 [59]; 2003-776923 [73]
DNN N2002-364678 DNC C2002-131331
TI Administering and distributing substance, e.g. pharmaceutically active agent, to target through bloodstream of organism by monitoring blood flow parameter(s), and adjusting distribution parameter.
DC A96 B05 B07 P31 S03 S05
IN KENSEY, K
PA (KENS-I) KENSEY K; (RHEO-N) RHEOLOGICS INC
CYC 97
PI US 2002032149 A1 20020314 (200249)* 46
WO 2002079778 A2 20021010 (200277) EN
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2002306461 A1 20021015 (200432)
ADT US 2002032149 A1 CIP of US 1997-919906 19970828, CIP of US 1999-439795 19991112, CIP of US 2000-501856 20000210, CIP of US 2000-628401 20000801, CIP of US 2000-727950 20001201, CIP of US 2001-819924 20010328, US 2001-841389 20010424; WO 2002079778 A2 WO 2002-US3984 20020207; AU 2002306461 A1 AU 2002-306461 20020207
FDT US 2002032149 A1 CIP of US 6019735, CIP of US 6322524, CIP of US 6322525; AU 2002306461 A1 Based on WO 2002079778
PRAI US 2001-841389 20010424; US 1997-919906 19970828;
US 1999-439795 19991112; US 2000-501856 20000210;
US 2000-628401 20000801; US 2000-727950 20001201;
US 2001-819924 20010328; US 2001-828761 20010409;
US 2001-839785 20010420
AB US2002032149 A UPAB: 20040520
NOVELTY - A substance (I) is administered and distributed (to a target) through a bloodstream of an organism by monitoring a blood flow parameter(s) of the bloodstream, after which a distribution parameter is adjusted by altering the parameter(s).

DETAILED DESCRIPTION - A substance (I) is administered and distributed (to a target) through a bloodstream of an organism by monitoring a blood flow parameter(s) of the bloodstream, after which a distribution parameter is adjusted by altering the parameter(s). The parameter is circulating blood, absolute, effective, low shear or high shear viscosities, shear rate of circulating blood, work of heart, contractility of heart, thrombogenicity, platelet aggregation, lubricity, red blood cell deformability, thixotropy, yield stress, coagulability, coagulation time, agglutination, clot retraction, clot lysis time, sedimentation rate, or prothrombin rate.

USE - The method is used for distributing and administering a substance, e.g. pharmaceutically active agent, through a bloodstream of an organism such as a human. It is used for utilizing the viscosity of the circulating blood of a living being, for diagnostics and treatment.

ADVANTAGE - The method provides data in a short span of time, with minimal invasiveness, and without the need to directly measure pressure, flow, and volume.

Dwg.0/22

L13 ANSWER 12 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-372354 [40] WPIDS
DNC C2002-105446
TI Production of **nateglinide** B-form **crystals** containing no H-form **crystals**, by drying wet **crystals** of **nateglinide** solvate at low temperature until solvent disappears and performing **crystal** transformation.
DC B05
IN MARUO, M; MATSUZAWA, Y; MIYAZAKI, K; NISHINA, S; SUMIKAWA, M
PA (AJIN) AJINOMOTO CO INC; (AJIN) AJINOMOTO KK
CYC 98
PI WO 2002034713 A1 20020502 (200240)* JA 9
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001096001 A 20020506 (200257)
EP 1334964 A1 20030813 (200355) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2003059212 A 20030707 (200377)
US 2003229249 A1 20031211 (200382)
BR 2001014846 A 20040225 (200416)
JP 2002537707 X 20040304 (200417)
MX 2003003575 A1 20030701 (200423)
CN 1483018 A 20040317 (200437)
ADT WO 2002034713 A1 WO 2001-JP9293 20011023; AU 2001096001 A AU 2001-96001 20011023; EP 1334964 A1 EP 2001-976819 20011023, WO 2001-JP9293 20011023; KR 2003059212 A KR 2003-705671 20030424; US 2003229249 A1 Cont of WO 2001-JP9293 20011023, US 2003-421888 20030424; BR 2001014846 A BR 2001-14846 20011023, WO 2001-JP9293 20011023; JP 2002537707 X WO 2001-JP9293 20011023, JP 2002-537707 20011023; MX 2003003575 A1 WO 2001-JP9293 20011023, MX 2003-3575 20030423; CN 1483018 A CN 2001-821299 20011023
FDT AU 2001096001 A Based on WO 2002034713; EP 1334964 A1 Based on WO 2002034713; BR 2001014846 A Based on WO 2002034713; JP 2002537707 X Based on WO 2002034713; MX 2003003575 A1 Based on WO 2002034713
PRAI JP 2000-324375 20001024
AB WO 200234713 A UPAB: 20020626
NOVELTY - Production of **nateglinide** (N-(trans-4-isopropyl-cyclohexane carbonyl)-D-phenylalanine) B-form **crystals** containing no H-form **crystals**, comprises drying wet **crystals** of **nateglinide** solvate at a low temperature until the solvent disappears and performing **crystal** transformation.
ACTIVITY - Antidiabetic.
MECHANISM OF ACTION - None given.
USE - The **nateglinide** B-form **crystals** containing no H-form **crystals** are used as diabetes medicines.
ADVANTAGE - The **nateglinide** B-form **crystals** containing no H-form **crystals** can be produced on an industrial scale at low cost.
Dwg.0/0

L13 ANSWER 13 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-372336 [40] WPIDS
DNC C2002-105445
TI New composition comprises **nateglinide** in the amorphous state,

useful for treatibg diabetes.
DC B05
IN MAKINO, C; NINOMIYA, N; YABUKI, A
PA (AJIN) AJINOMOTO CO INC; (AJIN) AJINOMOTO KK
CYC 98
PI WO 2002034254 A1 20020502 (200240)* JA 29
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001095999 A 20020506 (200257)
EP 1334720 A1 20030813 (200355) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2003042027 A 20030527 (200361)
BR 2001014896 A 20030812 (200367)
US 2004014815 A1 20040122 (200407)
CN 1482903 A 20040317 (200437)
ADT WO 2002034254 A1 WO 2001-JP9291 20011023; AU 2001095999 A AU 2001-95999 20011023; EP 1334720 A1 EP 2001-976817 20011023, WO 2001-JP9291 20011023; KR 2003042027 A KR 2003-705634 20030423; BR 2001014896 A BR 2001-14896 20011023, WO 2001-JP9291 20011023; US 2004014815 A1 Cont of WO 2001-JP9291 20011023, US 2003-421898 20030424; CN 1482903 A CN 2001-821217 20011023
FDT AU 2001095999 A Based on WO 2002034254; EP 1334720 A1 Based on WO 2002034254; BR 2001014896 A Based on WO 2002034254
PRAI JP 2000-324373 20001024
AB WO 200234254 A UPAB: 20020626
NOVELTY - Composition comprising **nateglinide** in the amorphous state, is new.
ACTIVITY - Antidiabetic. In oral bioavailability studies in beagles amorphous **nateglinide** had an AUC (mu g/ml.hr) of 22.29, a Cmax (mu g/ml) of 9.46 and a Tmax (hr) of 0.38. The corresponding values for **nateglinide crystalline** form H were 20.53, 8.93 and 0.38 respectively.
MECHANISM OF ACTION - None given.
USE - As preparations for administering **nateglinide** useful as an antidiabetic agent.
ADVANTAGE - Have rapid release properties.
Dwg.0/9

L13 ANSWER 14 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-290407 [30] WPIDS
CR 2003-401332 [38]
DNC C2001-088908
TI Use of a combination of **nateglinide** with another antidiabetic compound for treating a metabolic disorder, e.g. diabetes and associated conditions, or for effecting weight loss.
DC A96 B05
IN ALLISON, M; GATLIN, M R; GUITARD, C; KARNACHI, A A; MANNION, R O; PONGOWSKI, M; BALL, M; KAMACHI, A A; BALL, M A
PA (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERW GES MBH; (ALLI-I) ALLISON M; (BALL-I) BALL M A; (GATL-I) GATLIN M R; (GUIT-I) GUITARD C; (KARN-I) KARNACHI A A; (MANN-I) MANNION R O
CYC 95
PI WO 2001021159 A2 20010329 (200130)* EN 60
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM

DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

FR 2798592 A1 20010323 (200130)
FI 2001000683 A 20010515 (200140)
AU 2000079044 A 20010424 (200141)
CZ 2001001723 A3 20010815 (200157)
MX 2001004255 A1 20010801 (200238)
EP 1212077 A2 20020612 (200239) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
NO 2002001197 A 20020516 (200240)
BR 2000014525 A 20020611 (200248)
SK 2002000360 A3 20020702 (200253)
BE 1013726 A5 20020702 (200257)
KR 2002038758 A 20020523 (200274)
JP 2003509457 W 20030311 (200319) 83
US 2003162816 A1 20030828 (200357)
NZ 517280 A 20040227 (200418)
ZA 2002002107 A 20040331 (200426) 86

ADT WO 2001021159 A2 WO 2000-EP9074 20000915; FR 2798592 A1 FR 2000-11782 20000915; FI 2001000683 A WO 2000-EP9074 20000915, FI 2001-683 20010402; AU 2000079044 A AU 2000-79044 20000915; CZ 2001001723 A3 WO 2000-EP9074 20000915, CZ 2001-1723 20000915; MX 2001004255 A1 MX 2001-4255 20010427; EP 1212077 A2 EP 2000-969260 20000915, WO 2000-EP9074 20000915; NO 2002001197 A WO 2000-EP9074 20000915, NO 2002-1197 20020311; BR 2000014525 A BR 2000-14525 20000915, WO 2000-EP9074 20000915; SK 2002000360 A3 WO 2000-EP9074 20000915, SK 2002-360 20000915; BE 1013726 A5 BE 2000-585 20000915; KR 2002038758 A KR 2002-703551 20020316; JP 2003509457 W WO 2000-EP9074 20000915, JP 2001-524585 20000915; US 2003162816 A1 Provisional US 1999-240911P 19990917, Provisional US 2000-240918P 20000309, Provisional US 2000-304196P 20000407, Cont of US 2000-663264 20000915, US 2003-345908 20030116; NZ 517280 A NZ 2000-517280 20000915, WO 2000-EP9074 20000915; ZA 2002002107 A ZA 2002-2107 20020314

FDT AU 2000079044 A Based on WO 2001021159; CZ 2001001723 A3 Based on WO 2001021159; EP 1212077 A2 Based on WO 2001021159; BR 2000014525 A Based on WO 2001021159; SK 2002000360 A3 Based on WO 2001021159; JP 2003509457 W Based on WO 2001021159; NZ 517280 A Div in NZ 528738, Based on WO 2001021159

PRAI GB 2000-21055 20000826; US 1999-398364 19990917; US 2000-545480 20000407

AB WO 200121159 A UPAB: 20040421

NOVELTY - **Nateglinide** (I), optionally in combination with another antidiabetic compound, can be used in the treatment of diabetes and associated conditions. The combination can also be used for effecting weight loss.

DETAILED DESCRIPTION - Use of a combination of **nateglinide** (I) and at least 1 other antidiabetic compound, selected from thiazolidine derivatives (glitazones), sulfonyl urea derivatives and metformin, present in the free form or as salts, for prevention, delay of progression or treatment of metabolic disorders, or for cosmetic treatment to effect a loss of body weight, is new.

INDEPENDENT CLAIMS are included for the following:

(a) a combination of (I) with an antidiabetic compound (as described above) for simultaneous, sequential or separate use;

(b) compositions comprising (I) with the antidiabetic compound; and

(c) a composition capable of being granulated in the presence of water without the need for a subsequent pulverization step prior to tabletting, comprising (I) and a carrier; and its use for treating a metabolic disorder.

ACTIVITY - Antidiabetic; anorectic; antilipemic; opthalmological; vasotropic; antiulcer; antiinflammatory; cardiant; hypotensive; antianginal; dermatological; antiarthritic; osteopathic; gastrointestinal.

MECHANISM OF ACTION - None given.

USE - For treating a metabolic disorder, e.g. diabetes (particularly type II diabetes mellitus) and associated conditions, also for effecting weight loss. The compositions can be used to treat e.g. hyperglycemia, hyperinsulinemia, hyperlipidemia, insulin resistance, impaired glucose metabolism, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulonephritis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis, ulcerative colitis, coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, skin and connective tissue disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis, and conditions of impaired glucose tolerance.

Dwg.0/0

L13 ANSWER 15 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-281809 [29] WPIDS
DNC C2001-085742
TI Combination used for treating diabetes and metabolic disorders comprises **nateglinide**, antidiabetic phenylacetic acid derivative or acarbose and carrier.
DC B05
IN BALL, M; DUNNING, B; GATLIN, M R; PONGOWSKI, M
PA (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERW GES MBH
CYC 95
PI WO 2001026639 A2 20010419 (200129)* EN 28
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001011339 A 20010423 (200147)
EP 1218015 A2 20020703 (200251) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2001026639 A2 WO 2000-EP9816 20001006; AU 2001011339 A AU 2001-11339 20001006; EP 1218015 A2 EP 2000-972695 20001006, WO 2000-EP9816 20001006
FDT AU 2001011339 A Based on WO 2001026639; EP 1218015 A2 Based on WO 2001026639
PRAI US 1999-415308 19991008; US 1999-415307 19991008
AB WO 200126639 A UPAB: 20010528

NOVELTY - Combination (I) comprises **nateglinide**, an antidiabetic phenylacetic acid derivative or acarbose or their salts and optionally at least one carrier for simultaneous, separate or sequential use.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a commercial package comprising (I) together with instructions for the delay of progression or treatment of metabolic disorders or a method of improving bodily appearance.

ACTIVITY - Antidiabetic; antilipemic; antiulcer; antiinflammatory; vasotropic; hypotensive; cardiant; antiarthritic; osteopathic; cerebroprotective; anorectic; gastrointestinal; ophthalmological; muscular; dermatological.

MECHANISM OF ACTION - None given.

USE - Used for treating diabetes, conditions associated with diabetes, especially type 2 diabetes mellitus and metabolic disorders e.g. hyperglycemia, hyperinsulinaemia, hyperlipidemia, insulin resistance, impaired glucose metabolism, obesity, diabetic retinopathy, macular

degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis and ulcerative colitis, coronary heart disease, hypertension, angina pectoris, myocardial infarction, stroke, skin, connective tissue disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis and conditions of impaired glucose tolerance.

ADVANTAGE - The **nateglinide** and phenylacetic acid derivative show a synergistic effect.

Dwg.0/0

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